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Evidence- and consensus-based practice guidelines for the therapy of primary myelodysplastic syndromes. A statement from the Italian Society of Hematology

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Background and Objectives. Novel therapeutic agents and strategies have been introduced into the management of myelodysplastic syndromes (MDS) in the last years. This has led to more treatment options and a better chance of long-term survival for MDS patients, but also to uncertainty regarding the optimal use and possible side effects of these treatments. The Italian Society of Hematology commissioned a project to develop guidelines for the therapy of MDS using evidence-based knowledge and consensus-formation techniques.

Design and Methods. An Advisory Council (AC) shaped the project around a series of key clinical questions, performed a systematic search for evidence and graded the available evidence according to the Scottish Intercollegiate Guidelines Network (SIGN). A list of clinical questions was mailed to each of 10 senior hematologists composing the Expert Panel (EP): the panelists were asked to rank the most relevant questions, and to formulate answers to the questions according to the tables of evidence. A scenario phase followed, so as to reach a consensus on the three top ranked questions. The EP was asked to score patient profiles as appropriate or not appropriate for the therapeutic strategy under scrutiny, according to the RAND technique. Finally, from September 2001 to January 2002, four Consensus Conferences conducted according to the Nominal Group Technique were held in Milan, Italy. The overall goal of the conferences was to take a final decision upon the appropriateness of the uncertain scenarios and of the uncertain responses to the clinical questions.

Results. Evidence was judged sufficient for providing recommendations on the use of allogeneic stem cell transplantation, leukemia-like chemotherapy, autologous stem cell transplantation, low-dose chemotherapy, danazol, immunosuppressive therapy, hypomethylating agents and hematopoietic growth factors. Specific recommendations for supportive therapy, including iron chelation, were issued. Allogeneic stem cell transplantation was unanimously considered as the only curative treatment for MDS patients, and recommendations on its use were agreed based on patient's age, risk, clinical features and donor availability. AML-like chemotherapy was also considered a valuable therapeutic option for subsets of MDS patients. Autologous stem cell transplantation was recommended for patients who lack an HLA identical donor and have achieved complete remission with AML-like chemotherapy. Decitabine, recombinant human erythropoietin and immunosuppressive therapy were judged valuable therapeutic options for subsets of MDS patients whereas low-dose cytarabine was not. Specific therapeutic strategies for those subjects younger than 18 years or older than 75 years and the strategy of *watchful waiting* were decided by patient-oriented questions.

Interpretation and Conclusions. Using evidence and consensus, recommendations for the treatment of MDS were issued. Statements were graded according to the strength of the supporting evidence and uncertainty was explicitly declared.

Key words: myelodysplastic syndromes, guidelines, chemotherapy, stem cell transplantation, supportive therapy.

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Myelodysplastic syndromes (MDS) are clonal hematopoietic stem cell disorders characterized by ineffective hematopoiesis, peripheral cytopenias and substantial risk of progression to acute myeloid leukemia. They typically occur in elderly people with a median age at diagnosis ranging between 60 and 75 years in most series, with an incidence in patients aged 70 years and older greater than 20 cases in 100,000 people/year.[1]

Because of continuing research into new treatment methods, patients with MDS now have more therapy options and a better chance of long-term survival than ever before. However, data regarding the efficacy and safety of new therapies are based on small, uncontrolled, non-comparable case series; thus, physicians facing an individual patient with MDS have to rely on decisions based on their own experience and on anecdotal literature.

Perceiving the need for rigorous, consistent, and feasible recommendations for the management of patients with MDS, in an effort to optimize the identification of improved MDS treatment strategies, and to assess the quality of the data on existing treatment paradigms, the Italian Society of Hematology commissioned a *Consensus Conference* (CC) on the management of MDS. The aim of this work was to develop evidence- and consensus-based guidelines to provide clinicians direction on the usage of the currently available therapeutic strategies.

Design and Methods

The development of the guidelines was a multistep process. A 4-member *Advisory Council* (AC) was constituted in June 2001: it was composed of a hematologist with experience and interest in MDS, a statistician, and two clinical epidemiologists. The objectives of the AC were: 1) to define the goals of the project and to frame the operative context (need-assessment phase); 2) to systematically review the literature for the therapy of MDS (the systematic review phase); 3) to organize the consensus development process aimed at providing guidelines for the therapy of MDS (the consensus phase).

An *Expert Panel* (EP) was selected by the AC. The composition of the EP was determined according to the conceptual framework elements of the *NIH Consensus Development Program*. The Panel comprised ten physicians experienced in chemotherapy and/or transplants, adult or pediatric hematology and active both in care of patients and clinical research. Both academic and non-academic experts were included. The panel bias was minimized by eliminating from consideration strong advocates for or against one specific therapy. Each panelist signed a statement that they had no financial conflict of interest in performing this work and a pledge of objectivity before final appointment and acceptance of the position. Each panelist agreed to address some of the questions, according to their specific expertise.

Need-assessment phase

After three successive meetings and much free discussion, the AC, under the leadership of the *Prime Organizer* (ST), agreed on the goal of the project: "*to provide clinical practice recommendations that can support the appropriate choice of therapeutic interventions in patients with primary MDS, both of adult and pediatric age*". The AC also stated that the objective of these guidelines was to issue recommendations for therapies that addressed problems specifically presented by MDS patients, not common problems of hematologic disorders, such as infections or chemotherapy-induced neutropenia.

The AC decided to shape the guidelines around a list of key clinical questions. In quest for completeness, three different categories of questions were issued: patient-oriented, therapy-oriented and community-oriented questions. The AC submitted the EP a set of questions under the three aforementioned headings. Therapy-oriented questions pointed to the possible and recommendable strategies within each therapeutic category, to the possible and optimal candidates for a certain therapeutic strategy and to the risks deriving from that therapy.

A questionnaire was mailed to each panelist asking the panelist to rank the top choice among the questions proposed by the AC. Once the questionnaires had been returned, the questions were ranked according to their priority votes.

Systematic review phase

The AC and an expert librarian systematically retrieved literature according to four categories: indexed original papers, indexed reviews and educationals, abstract of conference proceedings, and ongoing trials. Indexed papers and reviews were identified through computerized search of the available bibliographic databases: PubMed (July 2001), the *Cochrane Register of Systematic Reviews*, *EMBASE*, *Current Contents* (July 2001). Boolean searches for *Myelodysplastic syndromes/*therapy* [MeSH]* OR *Myelodysplastic Syndromes [MeSH] AND Treatment Outcome [MeSH]* were performed on 31th July 2001 and limited to English-language publications edited after 1980. Articles published in letter formats were initially excluded, but the *related articles* function of PubMed was used to identify more citations. The citations retrieved by the above described query were first screened for their accuracy (papers describing populations with acute leukemias were excluded) and then exported to text files. A specific bibliographic database was built by importing PubMed records into a Reference Manager 8.0 archive (*MDS database*). The completeness of the data-base was investigated through manual check of the reference lists for each review article and for the papers indexed through 1999-July 2001.

Conference proceedings were manually retrieved and paper copies of the relevant abstracts were prepared, yet they were not recorded into the MDS database. The following proceedings were examined: American Society of Hematology, 2000 and 2001; European Society of Haematology, 2001; International Conference on Myelodysplastic Syndromes, 2001; American Society of Clinical Oncol-

ogy, 1999, 2000, and 2001.

Ongoing or finished but as yet unpublished trials registered at the NCI web site and addressing patients with MDS were selected and the protocol description was downloaded. All the MDS database records were classified according to the question they addressed. Paper copies of review articles and selected relevant original papers were collected.

Two reviewers, a member of the AC and one of the EP, filled a review form for each relevant paper. The form included a full description of the enrolled populations, design of the study, outcomes and outcomes predictors. Papers were excluded from analysis if they included fewer than 3 patients with a MDS according to the WHO classification system. Translated evidence was not fully reviewed but extrapolations were made by the panelists as appropriate. A final judgment of the quality of evidence was agreed by the two reviewers, according to the statements of the Scottish Intercollegiate Guidelines Network (SIGN).[2] Briefly, randomized studies, systematic reviews or meta-analyses were graded 1, longitudinal studies were graded 2 and case series 3. Finally, each clinical question was provided with a table of evidence that synthesized the pertaining literature.

Consensus Phase

Recommendation elaboration. The panelists formulated proper evidence-based statements for each assigned question. Final recommendations for the assigned therapeutic category were also formulated and ranked according to the supporting evidence level. Level A recommendations were supported by grade 1 studies, level B by grade 2 studies, level C by grade 3 studies and level D by expert judgment, according to the SIGN classification method.[2] Subsequently, each panelist scored his/her agreement with the statements made by the other panelists (score from 1 to 9) and provided suggestions for rephrasing.

Scenario analysis. Scenario analysis was used to reach a consensus on the top ranked questions of the questionnaire, besides the frontiers of evidence. Since the three top ranked questions were: *Which patient does not need any treatment and can be just followed ? For which patients is allogeneic stem cell transplantation an appropriate therapy? For which patients is leukemia-like chemotherapy an appropriate therapy?* using a technique developed at the RAND Corporation,[3] panelists were asked to rate the appropriateness of these three therapeutic strategies among different populations of patients. The parameters relevant to therapy choice were singled out by the experts and were permuted to define from 40 to 52 scenarios. The number of clinical scenarios was always lower than all the theoretically possible combinations: some were not rated because the AP judged them unlikely to occur, while others were fused because of redundancy. Panelists were instructed to rate the appropriateness of the therapeutic strategy in each clinical scenario according to their clinical experience and scientific knowledge. Appropriateness was scored on a scale from 1 to 9, where 1 indicated that the questioned strategy was totally inappropriate and 9 indicated that it was totally appropriate. *Appropriate* meant that the expected adverse effects of that strategy were less than the expected adverse effects of avoiding that intervention (or non-intervention). *Inappropriate* was defined as the converse. Panelists were instructed to exclude cost and participation in clinical trials as reasons to rate scenarios as either appropriate or inappropriate.

Median appropriateness score and mean absolute deviation from the median were calculated for each setting (specific intervention in a specific scenario). An appropriateness index was then calculated.[4] For each intervention, the relationship of the appropriateness index to the permutated clinical variables that defined the scenarios was analyzed in 2 ways: ANOVA and recursive partitioning, a non-parametric method for exploratory data analysis and summarization. ANOVA was used to determine the fraction of variance in the appropriateness index explained by each clinical variable. Recursive partitioning was used to develop a treatment algorithm. If the mean appropriateness index was below 3.5, the examined intervention was considered not appropriate in that group of scenarios; conversely, if the index was above 6.5, the intervention was considered to be appropriate. The indication for an intervention was deemed uncertain when the index fell between 3.5 and 6.5. The resulting trees were pruned with the method of 10-fold cross validation to avoid overfitting of the data. Because the regression tree selected the best of all possible splits, we applied a Bonferroni multiple comparison correction to the *p*-values.

Nominal group technique. In this phase, the EP was convened and four consensus conferences were held in Milan, Italy, between September 2001 and January 2002. The meetings were attended by the 10 panelists with the assistance of the AC. The overall goal of the meetings was to reach a definite consensus on question-specific statements and to agree on the appropriateness of some selected scenarios: the statements and the scenarios to be discussed

were selected because of disagreement during the first-round postal phase. The nominal group technique[5] was used to solve any residual disagreement on the selected items. Participants were first asked to comment in round-robin fashion on their pre-meeting votes and then to propose a new vote. If an 80% consensus on the issue (scenario or statement) was not achieved, the choices were discussed and a second vote taken. If an 80% consensus was still not attained, the issue was declared undecidable and no further attempt was made.

Diffusion and implementation

The AC and the EP agreed on the diffusion plan of the guidelines. A full report will be submitted to the National Clearinghouse that holds the largest guidelines repository. Scientific societies, as well as the *European Agency for the Evaluation of Medical Products* (EMEA) and SIGN will be notified with a full report of the guidelines. The recommendations will be fully explorable through an interactive query at the official site of Haematologica (*http://www.haematologica.org*). These guidelines are intended to expire in 2004. An update by a consensus meeting is planned for the first half of 2003.

Results

After reviewing the proposed classifications and risk staging systems, the EP agreed on the adoption of the WHO classification[6] and IPSS risk score,[7] to be used throughout the project. Thus, the formerly FAB-classified refractory anemia with excess blasts in transformation (RAEB-t) was not a target of these guidelines, as were not the myeloproliferative/myelodysplastic syndromes, such as chronic myelomonocytic leukemia, atypical chronic myeloid leukemia and juvenile chronic myelomonocytic leukemia.

The key therapy questions

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

Provided that no therapy can prolong life without causing side effects, the EP agreed that abstaining from giving treatment may be a rational way of managing certain categories of patients. Similarly, the EP agreed that agents committed to modifying patients' quality of life can be appropriately spared in those patients who would not get a benefit from the therapy. Literature comparing disease-modifying therapies with no treatment is currently lacking. Thus, scenario analysis was performed to define the categories of patients suitable for being followed-up without therapy. Age, performance status, severity of anemia and IPSS risk class were considered as relevant features upon which to decide the clinical conduct. Age ($F=21.21$; $p<0.001$) and severity of anemia ($F=2.11$; $p<0.05$) were significantly correlated with the appropriateness index. These 2 parameters explained 80% of the variance of appropriateness rating at linear multivariate analysis.

The first split made by the recursive partitioning algorithm was based on age. Subjects aged lower than 65 years, regardless of other characteristics, had a lower mean appropriateness rating than older subjects ($p<0.001$). The algorithm next split patients both aged younger and older than 65 years according to anemia and IPSS risk class. Indeed, those subjects older than 65 years and with moderate to mild anemia (Hb higher than 8 g/dL) and a low IPSS risk class had a higher appropriateness rating and were thus judged suitable for no treatment (mean appropriateness rating =7.7). Those subjects aged younger than 65 years, with mild anemia (Hb higher than 10 g/dL) and a low IPSS risk class had a higher appropriateness rating and thus were judged suitable for no treatment. Further splits were either not statistically significant, clinically unrelevant or both.

The Panel agreed on the following recommendations:

- *patients do not need any treatment and can be just followed if they are over 65 years old, the IPSS risk is low and anemia is moderate or mild (Hb higher than 8 g/dL) (Recommendation level D);*
- *patients younger than 65 years do not need any treatment when the IPSS risk is low and anemia is mild (Hb higher than 10 g/dL) (Recommendation level D);*
- *no child with MDS can be considered at low IPSS risk, thus all children need treatment (Recommendation level D).*

If not treated, how should patients be monitored and managed?

The EP agreed that patients must understand that a decision to forgo therapy is considered safe only if the patient and the physician remain committed to conscientious monitoring. The goals of such follow-up include the early recognition of worsening anemia, increasing number of circulating blasts, and the appearance of cytogenetic alterations.

In the absence of literature-based evidence, the EP recommended that:

- *when not treated, the patient should have a full blood count and physical examination at least every three months. Annually, he/she should undergo a bone marrow examination for blast count and cytogenetics (Recommendation level D).*

Which patients are candidates for HLA typing?

Typing a patient along with his or her siblings for HLA is a way of obtaining information on the possibilities a patient has to proceed to stem cell transplantation from a related donor. Knowing that there is a fully compatible sibling informs both physician and patient that a potentially life-saving procedure may be performed.

Appropriateness of typing for HLA is not completely equivalent to appropriateness of performing stem cell transplantation. Absence of a compatible sibling donor may direct the front-line therapy in younger patients, even before having decided about transplant appropriateness. In the absence of literature dealing with the problem of appropriateness of HLA typing, the EP agreed that decisions must be founded on clinical judgment on a case-by-case basis. Scenario analysis was performed to define the patient categories worth being typed. The EP agreed that age, performance status, IPSS risk categories and cytogenetics were relevant features upon which to decide whether to conduct HLA typing. Forty selected scenarios were administered to the EP. Age ($F=572.2$; $p<0.001$) and ECOG score of performance status ($F=5.010$; $p=0.026$) were significantly correlated with appropriateness rating and explained 85% of the appropriateness variability. The first split made by the recursive partitioning algorithm was based on age. Subjects aged lower than 55 years, regardless of other characteristics, had a higher mean appropriateness rating (8.73) than those with older age (rating 3.08; $p<0.001$). Patients older than 55 years were further split by the algorithm into subgroups according to their age. Subjects over 65 years old had a much lower appropriateness index (1.5) than those aged from 60 to 65 years (3.17) or from 55 to 60 years (4.56). Subjects aged from 55 to 60 years were further split according to ECOG performance status. As a matter of fact, those patients who had a preserved good performance status (ECOG 1-2), had a high appropriateness index (7.0). Further splits were either not statistically significant, clinically unimportant or both. The Panel agreed on the following recommendations:

- *for patients under 55 years old, HLA typing of the patient and siblings is recommended, irrespectively of the former's risk class or performance status (Recommendation level D);*
- *for patients more than 55 years old but less than 65 years old, HLA typing is recommended only for those with a good performance status (ECOG 1-2) (Recommendation level D).*

Which adult patients are candidates for allogeneic stem cell transplantation?

Allogeneic stem cell transplantation (allo-SCT) is the only known curative treatment in MDS. Evidence regarding allo-SCT was collected by analyzing 45 studies. One randomized controlled trial provided level 1^- evidence[8] and 11 non-randomized (observational) controlled reports provided level 2 evidence. The largest series was reported by the EBMT group[9] and comprised 712 patients with WHO-defined MDS. The second largest series came from the Fred Hutchinson Cancer Center, Seattle, and comprised 221 WHO-defined MDS.[10] Only 4 additional studies reported more than 50 cases of WHO-defined MDS. Overall, 4402 patients were reported in the analyzed studies: a refractory anemia constituted 15%, and secondary MDS constituted 21% of the diseases in the overall population in the 15 studies that reported a breakdown of the enrolled population. Twenty-six studies reported overall 1122 patients transplanted from an unrelated donor. The median disease duration in the enrolled MDS patients was longer than 10 months in 4 studies and longer than 6 months in 12.

Randomized trials comparing conventional-dose chemotherapy versus high-dose therapy and transplant in adults with MDS are currently lacking. Thus, subject selection and time-to-treatment biases from non-randomized studies precluded definite conclusions on the expected survival. Based upon available data, expected survival 4 years after transplantation ranged from 30% to 40% (evidence from level 2^+ to 3) and was stable even after longer follow-up times (evidence 2^-): this indicated that about one third of patients with MDS could be cured by allo-SCT.

Older age was related to a shorter overall survival (OS) and disease-free survival (DFS) (evidence from level 2^{++} to 3), due to the higher transplant-related mortality (TRM) (evidence 2^+). Survival was also higher in those patients with complex abnormalities of chromosome 7 (49%) with respect to those without (16%) (evidence 2^+). When cytogenetic subgroups were classified according to IPSS, OS at 3 years was over 50% in low- or intermediate-risk patients and 30% in high-risk patients (evidence 2^+).

Disease phenotype and risk class were correlated with survival. DFS was about twice as long in those patients with refractory anemia (RA) at transplantation: such patients have an expected rate of cure as high as 73%.[11] Similarly, IPSS risk showed an inverse correlation with relapse-free survival after transplantation. Retrospective studies of homoge-

neous populations reported that DFS at 5 years was 60% in patients with risk low or INT-1, while it was 36% to 44% in those belonging to the INT-2 risk class and 28% to 30% in high-risk patients (evidence 2^+).

The need for pre-SCT remission induction chemotherapy remains a contentious issue: European centers generally administered remission-induction treatment prior to SCT, while North American centers did not. Randomized controlled trials are currently lacking. The EBMT, *Chronic Leukemia Working Party*, launched a prospective randomized multicenter study with the purpose of evaluating the potential benefit of achieving a complete remission after a remission-induction and consolidation chemotherapy before allogeneic transplantation using HLA identical sibling donors. In observational studies, the DFS of those patients who did not receive chemotherapy was 58% and 75% in RA and RA with excess blasts (RAEB) at 2 years, respectively, while those patients who underwent allo-SCT while in remission after chemotherapy had an expected 2-year DFS of 60% (evidence 2^-) and an OS of 45% (evidence 2^-).[12] The 5-year DFS and OS for the entire population of MDS patients was 34% and 41%, respectively.[13] The non-relapse-related mortality (NRM), i.e. including the later deaths due to chronic graft-versus-host disease (GVHD), ranged from 29% to 68%. Lower age was associated with a lower TRM at both univariate and multivariate analyses, and was 32% in patients younger than 37 years, and 67% in those older than 37 years. A shorter disease duration was related to TRM at multivariate analysis of the 200 MDS patients transplanted in Seattle.[10] Male sex was significantly associated with TRM (evidence 2-) at multivariate analysis with a relative risk of TRM over 2.

In low-risk patients, the association of busulfan (Bu), cyclophosphamide (Cy) and total body irradiation (TBI) did not lead to an increased NRM, while this occurred in high risk patients: 68% of the high-risk patients treated with Bu-Cy-TBI incurred NRM vs 36% of those treated with Cy-TBI (p =0.12).

No advantage of peripheral stem cell on DFS was demonstrated by a randomized clinical trial comparing peripheral with bone marrow stem cells transplantation (evidence 1^+).[8] However, in-hospital mortality was shown to be lower and lenght of stay shorter in recipients of peripheral stem cells (16% vs 23% and 15 days vs 20-30 days, respectively).[14]

Allo-SCT from unrelated donors was specifically addressed by 6 large studies that enrolled overall 158 patients. Two-year DFS was 28% to 35% and was somewhat similar between recipients of stem cells from unrelated donor or siblings. HLA match, however, was a statistically significant prognostic variable after multivariate adjustment.[15] Transplantation from unrelated donors led to a TRM of 48% to 58% in the two largest studies of a homogeneous MDS population;[16,17] TRM was greater in recipients of transplants from unrelated donors at multivariate analysis in one study.[18]

Disease relapse rate ranged from 13% to 19% in patients with WHO-defined MDS. Short disease duration and a favorable karyotype were important predictors of relapse at multivariate analysis.[19] The relapse rate was higher in patients with selected cytogenetic abnormalities, such as 5^-, 7, and 8^+; these patients had a relapse rate of 38% whereas those without any cytogenetic abnormality had a relapse rate from 14% to17%. Disease phenotype at diagnosis was important, since relapse rate was 0-8% in patients with RA/RA with ringed sideroblasts (RARS) (six studies, evidence from 2^+ to 2^{--}). Clinical trials are currently evaluating dose-modified preparative regimens with decreased toxicity, which offer transplantation options also to older patients and patients with comorbidities.

After discussion, the EP singled out the relevant features composing the appropriateness of allo-SCT. Emphasis was set on patient's risk aversion as an important determinant of the decision, so analysis focused on adults with MDS, 18-55-year old with a good performance score (ECOG 1-2) and a moderate risk aversion. Patient's age, IPSS risk class, performance status, severity of anemia and presence of neutropenia or of unfavorable cytogenetics were the determinants of the decision to recommened allo-SCT. The parameters were permuted so as to build clinical settings, forty-seven of which were offered to the EP for appropriateness scoring. The mean appropriateness rating for allo-SCT from HLA-identical siblings was 4.15 and the variables that correlated directly with the rating were: age ($F=409.1$; $p<0.001$) and ECOG performance status ($F=23.63$; $p<0.0001$). Together, the variables explained 84% of the variance of the scores. Indeed, the first split made by the recursive partitioning algorithm was based on age. Subjects under 55 years old had a mean appropriateness index of 6.5, while those older than 55 years had an appropriateness index of 2.36 ($F=982.6$; $p<0.001$). The algorithm's further splits were also based on age: subjects with an age lower than 55 but greater than 40 had a mean appropriateness rating that was lower than that of younger patients ($F=72.82$; $p<0.001$). The subsequent variable used by the recursive partitioning was IPSS risk score: an IPSS risk of INT-2 or high had

a higher mean appropriateness rating (4.5) than those with IPSS risk of INT-1 or low (F=6.76; $p<0.01$). Subjects under 40 years old and with an INT-1, INT-2 or high IPSS risk had a higher mean appropriateness rating (7.57) than those with low IPSS risk (7.0; F=5.32; $p=0.024$). The algorithm further split patients with IPSS low-risk class according to anemia and cytogenetics. Appropriateness of SCT transplantation was higher in patients with moderate to severe anemia or unfavorable cytogenetics, than in the related counterpart (F=8.46; $p=0.008$).

Appropriateness of allo-SCT from an unrelated donor was also investigated in a scenario analysis. Age and IPSS risk score explained 80% of the variability of appropriateness rating. Patients aged less than 40 years and with an INT-1 or high IPSS risk score, had a mean appropriateness rating of 8.75, while those patients with a low or INT-1 IPSS risk score had an appropriateness rating that depended upon ECOG performance status, cytogenetics and neutropenia. With a good performance status (ECOG 1-2), the appropriateness of allo-SCT from an unrelated donor was rated as 7.75.

The Panel agreed on the following recommendations:

- *the decision of allo-SCT should be shared with the patient, whose risk aversion and performance status should be taken into account (Recommendation level D);*
- *considering patients with a moderate risk aversion, allo-SCT from an identical sibling should be recommended to patients younger than 55 years with an IPSS risk class INT-1, INT-2 or high (Recommendation level B);*
- *patients under 40 years old with a low IPSS risk score are also candidates for allo-SCT if they have moderate or severe anemia (Hb lower than 10 g/dL) (Recommendation level D);*
- *allo-SCT from an unrelated donor should be recommended to patients younger than 40 years who do not have a related donor but are in IPSS risk class INT-1, INT-2 or high. Patients younger than 40 years with a low IPSS risk score are also candidates for allo-SCT from an unrelated donor when there is a good performance status (ECOG 1-2), unfavorable cytogenetics or severe neutropenia (Recommendation level D);*
- *peripheral stem cells are the recommended source of the allo-SCT (Recommendation level B);*
- *in patients who could be candidates for high dose chemotherapy, it is not recommended to precede allo-SCT with a course of chemotherapy (Recommendation level D);*
- *busulfan/cyclophosphamide conditioning regimen and a busulfan dose to achieve plasma levels of 600-900 ng/mL are recommended (Recommendation level C);*
- *no recommendations may be given at present on the use of allo-SCT with regimens of low intensity conditioning; the EP does, however, consider this a promising approach.*

Which patients are candidates for AML-like chemotherapy?

MDS have features similar to those seen in acute myeloid leukemia (AML) of advanced age, e.g., multilineage dysplasia and unfavorable karyotypes characterized by deletions, duplication and complex cytogenetic abnormalities. The prognosis of MDS patients with a high-risk prognostic score is also not dissimilar from that of patients with AML. These similarities have encouraged the application of AML-like therapeutic approaches designed to eradicate or suppress the abnormal clone by intensive chemotherapy, thereby inducing long-term complete remission, including cytogenetic remission.

Several studies have enrolled MDS patients to AML-like chemotherapy. Considering studies that enrolled at least three cases of WHO-classified MDS, 13 studies were reported in 15 papers with a total enrolment of 374 patients (from 4 to 62 each). The evidence grade of the studies ranged from 1– (3 randomized studies) to 2– (non-controlled observational studies). RAEB cases were usually analyzed in association with RAEB-t, and in 7 studies patients with CMMoL, which does not belong to the WHO definition of MDS, were also included. Patients with WHO-classified MDS represent 14%[19] to 98%[20] of the total reported population. Patients with RA and RARS were rarely enrolled in chemotherapy programs. The median age of patients studied ranged from 44 to 71 years, but the upper range of values was greater than 70 years in 11 studies. The median follow-up ranged from 4 to 17 months.

Standard doses of cytosine-arabinoside (ARA-C), defined as 100-200 mg/m^2 every 12-24 hours × 5-10 days, were associated with fludarabine in 2 studies, with idarubicin in 6 and with other anthracyclines in 5, for a total of 182 WHO-classified patients. The complete remission rate ranged from 19% to 79%, with a median value of 41%. The OS of patients varied from 7 to 15 months and their DFS from 4.5 to 18 months. Young age and low neutrophil count predicted survival after chemotherapy in one study (evidence 2–). The toxicity-related mortality ranged from 0% to 35%.

High or intermediate doses of ARA-C refer to dif-

ferent treatment schedules: 1.5 g/m^2 continuous infusion daily for up to 5 days; short infusion of 2-3 g/m^2 every 12-24 hours daily × 4-5 days; 0.5-1 g/m^2 per day up to 5 days or 3-5 g/m^2 over the course of treatment. These regimens were employed either alone or in association with fludarabine, idarubicin (IDA) or other anthracyclines in 8 studies for a total of 181 enrolled patients with WHO-classified MDS. The complete remission rate in the only study with ARA-C alone was 13%.[21] However, the complete remission rate was 48 to 78% with a median value of 62% in studies in which ARA-C was used in association.

The OS ranged from 7 to 13 months with a DFS from 5 to 15 months.[22] The response duration was from 6 to 64 months. Younger patients had a better response rate. Patients with a short disease duration (<3-6 months) had from 77% to 86% response compared to 25%-58% in patients with longer disease duration. The correlation of response with karyotype was uncertain: in some studies patients with a favorable karyotype had better response rates (54% to 57%) than those presenting with monosomy 5 or 7 (13% to 31%). Mortality due to toxicity, mainly hemorrhages or infection after chemotherapy, ranged from 0 to 10% in studies in which ARA-C was associated with fludarabine or IDA. Higher toxicity was reported in studies in which ARA-C was associated with mitoxantrone.[23]

There was no evidence that adding granulocyte colony-stimulating factor (G-CSF) reduced the infection rate after chemotherapy. Data on secondary MDS were insufficient to derive conclusions on this issue.

The use of agents capable of reverting the multidrug resistance phenotype, such as quinine, associated with AML-like chemotherapy proved to be useful in patients expressing P-glycoprotein (PGP phenotype), which was found in 40-70% of primary and previously untreated MDS. However, the evidence on the use of quinine was based on only 2 studies.[20] In one randomized trial (evidence 1$^-$),[23] patients with high risk MDS were randomized to receive mitoxantrone plus ARA-C with or without quinine. In PGP-positive cases, 13 of the 25 (52%) patients who received quinine achieved CR as compared to 3 of the 17 (18%) patients treated with chemotherapy alone (p=0.02).

Since those patients who cannot undergo allo-SCT might be candidates for AML-like chemotherapy, the EP was asked to score the appropriateness of AML-like chemotherapy in the same 40 scenarios that they had scored for allo-SCT. Age (F=39.4; p<0.001), ECOG performance status (F=27.8; p<0.001), and IPSS risk class (F=65.5; p<0.001) were correlated with appropriateness rating. The three variables explained 79% of the appropriateness variability. The recursive partitioning algorithm first split patients based upon IPSS risk class: those patients with a low or INT-1 risk had a mean appropriateness rating equal to 3.2, while those with a higher risk had an appropriateness rating of 6.2 (p<0.001). Age was the further discriminant factor: patients older than 65 years had a low mean appropriateness rating (3.0) despite an INT-2 or high IPSS risk class. Those younger than 65 years with an INT-2 or high IPSS risk class had a high mean appropriateness rating (8.3) if either ECOG perfomance status was good (1-2) or age was younger than 55 years.

The Panel agreed that:

- *AML-like chemotherapy is highly recommended for patients not candidates for stem cell transplantation, who are younger than 55 years and have an INT-2 or high IPSS risk score (Recommendation level A);*
- *AML-like chemotherapy is also recommended for patients aged between 55 years and 65 years with an INT-2 or high IPSS risk score and a good performance status (ECOG 0-1) (Recommendation level D);*
- *standard or high-dose ARA-C combined with anthracyclines or fludarabine are the recommended drug associations (Recommendation level B);*
- *no recommendation can be given on the use of hematopoietic growth factors (G-CSF or GM-CSF) and revertant drugs in association with chemotherapy (Recommendation level D).*

Which patients are candidates for autologous stem cell transplantation

The rationale for the use of autologous SCT (auto-SCT) in MDS is the feasibility of collecting normal polyclonal stem cells at the time of chemotherapy-induced remission. Evidence for the use of auto-SCT is based on data abstraction and analysis of 5 studies, most also including AML patients (evidence from 2^{--} to 2$^+$). Three studies reported more than 10 cases of WHO-defined MDS. Enrolled subjects had a median age of less than 45 years, all were in a complete remission obtained by high dose chemotherapy and all received a conditioning regimen containing busulfan and cyclophosphamide. Patients from the EBMT registry,[24] who received autologous marrow grafts in first complete remission, showed 2-year DFS and OS of 34% and 39%, respectively, while TRM and actuarial relapse rate were 19% and 64%, respectively. Age lower than 40 years was associated with significantly superior DFS (39% vs

25%). Hematologic reconstitution tended to be faster after autologous peripheral blood stem cell transplantation (PBSC) than after a bone marrow cell transplantation, although not significantly so, and PBSC collection yielded higher numbers of stem cells than marrow collection in some cases, thus improving the percentage of MDS patients autografted in CR.[25]

The EP concluded that:

- *autologous stem cell transplantation should be recommended for patients who lack an HLA identical donor and who attained a complete remission after AML-like chemotherapy (Recommendation level D).*
- *myeloablative conditioning and a peripheral source of hematopoietic stem cells are recommended (Recommendation level B).*

Appropriateness of disease-modifying therapies

Which patients are candidates for low-dose chemotherapy?

A treatment strategy based on the use of single cytotoxic agents, administered at low doses for a shorter or longer period of time, is employed as palliative treatment for those MDS patients who are considered unable to withstand the rigors of myelosuppressive treatments. The effectiveness of low-dose chemotherapy relies on the possibility of overcoming cellular differentiation arrest and inducing the production of normally functioning mature cells. The ways by which the differentiation-inducing agents actually work have remained largely unresolved and a myelosuppressive mechanism is also evident with such therapies. Low-dose subcutaneous cytarabine (ARA-C) and low dose oral melphalan have been both used and studies on them reported. Evidence on low-dose ARA-C as a single agent is based on 3 controlled trials (evidence from 1^{++} to 1^{-}), 11 phase I-II trials (evidence from 2^{--} to 2^{+}) and 18 series of a few cases (evidence 3). One hundred and forty-one patients were treated in a combined Eastern Cooperative Oncology Group and Southwest Oncology Group randomized phase III study evaluating low-dose ARA-C (10 mg/m^2 subcutaneously *bid*) versus supportive treatment.[26] The overall response rate to a single cycle of low dose ARA-C was 32%, with 11% complete and 21% partial responses. The median duration of response was 5.9 months, with a range of 1.4 to 33.5 months. Responses were seen in all WHO-classified subtypes of MDS. Infections were more common in the low-dose ARA-C arm in which, however, patients had a decreased transfusion requirement after 3 months. There was no difference in the time to progression or the overall survival for patients treated with low-dose ARA-C or supportive therapy. The incidence of leukemic transformation was similar in both arms at 15%, but differed according to the MDS subtype. A further trial randomized 98 consecutive patients with MDS to a treated or a control group, both receiving conventional supportive therapy.[27] The treated group was given 13-cis-retinoic acid, 20 mg/day if marrow blasts were less than or equal to 5% or ARA-C 10 mg/day subcutaneously on 6 days/week if marrow blasts were from 6% to 30%, to which retinoic acid was added after 12 weeks. Log rank analysis carried out after 25 months showed no significant difference in survival between the treated and control groups, either in the total patient population or in the high and low blast subgroups.

Review of the small series of cases was difficult because of the different doses used, selection of patients, duration of treatment and criteria of response. Pooling the data, the complete remission rate was 17%, while 19% of patients achieved partial remission. Myelosuppression was documented in 88% of patients and treatment-related mortality was reported in 15%. Evidence on the effects of low-dose melphalan derived from two studies, including an overall total of 42 patients. Melphalan at the dose of 2 mg/day was administered to patients with high risk MDS resulting in a 38% overall response rate with minimal toxicity (evidence 2^{+})[28] or to elderly patients with high risk MDS with a response rate of 40% (evidence 3).[29] The EP agreed that:

- *evidence is sufficient to recommend that low-dose ARA-C is not used because of the high risk of myelosuppression with low remission rates (Recommendation level B).*
- *evidence is not sufficient to make recommendations on the use of low-dose melphalan which should be restricted to experimental studies.*

Which patients are candidates for danazol?

Androgens are interesting agents in MDS because they carry both the potential of stimulating normal hematopoiesis and repressing the neoplastic clone. Danazol is an androgen derived from the progesterone ethysteone, i.e. a modified androgen. It acts as an immunomodulator, increasing the clearance of immune complexes and reducing the number of crystallizable fragment receptors on monocytes. Danazol, moreover, inhibits the production of interleukin-1 β and tumor necrosis factor, an effect sim-

ilar to that observed with glucocorticosteroids.

Data on the efficacy of the drug derive from one double-blind, placebo-controlled randomized trial,[31] and 11 phase I-II trials, with a total number of 309 reported cases. Fifty patients were randomized to receive a single oral dose of either danazol (600 mg/day) or matching placebo (evidence 1-). Nine of the patients treated with the drug had RA and 12 had RAEB. Complete response, i.e. Hb >12 g/dL, granulocyte count >1,500/μL and platelet count >150,000/μL was obtained in 6/23 of the danazol arm (26%) but in no patient in the placebo arm. No response stratification according to disease category was reported, neither were the individual pre-study hematologic values reported. In the only non-controlled series with consecutive cases, seventy-six patients were treated with danazol for 8.7 (range 1-72) months.[31] No change in blood count was reported. Only four patients had an increased platelet count: platelet antibodies were not predictive of the response. Reviewing the individual cases reported in literature, a response on platelet count was found in 69/202 evaluable patients, i.e a rate of 34%. However, responses were also defined as those in patients with moderate thrombocytopenia. In the only paper that evaluated the effect of danazol on severe thrombocytopenia, i.e with platelet counts lower than 50,000/μL,[32] a response was observed in 8/13 patients (61.5%), at the dose of 600 mg/day for at least 3 months.

In the comparative study from the Mayo Clinic, 48 patients with favorable MDS (RA or RARS) receiving danazol 800 mg for three months were compared with patients receiving 13-cis-retinoic acid at two different doses.[33] The authors found little response in both arms, with only 1 partial and 1 minor response to danazol among 34 cases (6%).

In no study was life expectancy or evolution to blast transformation evaluated as an outcome.

The EP agreed that evidence was sufficient to give some recommendations on the use of danazol. They concluded that:

- *danazol is not recommended as a therapy for improving anemia, leukopenia, life expectancy or evolution toward blast transformation (Recommendation level B);*
- *in patients with severe thrombocytopenia (platelet count lower than 50,000/μL) and not candidates for other therapies, a trial with danazol at the dose of 600 mg/day for no less than 4 months should be given (Recommendation level C);*
- *if no significant increase of platelet count is attained after four months (platelet count greater than 100,000/μL), the drug should be withdrawn (Recommendation level D);*
- *a monthly control of liver enzymes is warranted (Recommendation level D);*
- *no recommendations on the use of danazol associated with other drugs, such as erythropoietin, retinoic acid or prednisone, can be given.*

Which patients with MDS are candidates for 5-azacytidine or decitabine?

Hypermethylation of specific DNA sequences, thus suppression of gene transcription, has been implicated in the pathogenesis of MDS. Pyrimidine nucleoside analogs that strongly inhibit DNA methyl transferase activity have been proposed for treating MDS. Two nucleosides that affect this process have been tested in clinical trials: 5-azacytidine, a ring analog of cytidine, and decitabine (5-aza-2'-deoxycytidine).

Even though a clinical phase III trial is ongoing (*European Organization of Research and Treatment of Cancer -EORTC, Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto-GIMEMA*, and the *German MDS study group*), data on the efficacy of this drug category derive from one randomized clinical study published in abstract form, the CALBG phase III trial (evidence 1^-),[34] and a few phase I or I/II studies (evidence from 2^{--} to 2^+).

The CALBG cross-over trial involved 191 patients who were stratified and randomized for standard supportive care (n = 92) or subcutaneous azacytidine (n = 99) given at 75 mg/m^2/d × 7 days every 28 days × 4 cycles. Significant differences in complete remissions, partial remissions, and *improved* categories between the azacytidine-treated group and the group receiving only supportive care were evidenced, with low treatment-related mortality (<1%). The median duration of response was 15 months. A statistical analysis of competing variables demonstrated a significant difference in time to AML or death for those treated initially with azacytidine or supportive care (p=0.0034). Transformation to AML was 2.8-fold (p=0.003) greater in the supportive-care group than in the azacytidine group, suggesting that azacytidine can prevent transformation to acute leukemia. A quality-of-life analysis showed that patients initially treated with azacytidine had significantly greater improvements over time in fatigue, dyspnea, physical functioning, and physiological distress compared with those receiving supportive care only. One hundred and twenty-four patients were enrolled in 5 non-controlled studies whose quality was rated as good (evidence 2^+) in 2 and fairly good (evidence 2^-) in the others. The populations were heterogeneous, but most had a high risk disease and

an old age. Decitabine was used in four of the trials, at different infusion schedules, but with a total dose per cycle ranging from 120 to 150 mg/m^2. Azacytidine was used in the fifth study and doses ranged from 10-25 mg/m^2 for 14 days to 45 mg/m^2 for 3 days per week every 6 weeks. Consistently, the studies agreed on the efficacy of the drug in inducing response, rated, using different response criteria, from 47% to 50%.

Stratifying patients by the IPSS risk score, response rates increased up to 64%, going from intermediate to high risk (evidence 2$^+$). In patients with clonal chromosomal abnormalities, major cytogenetic responses were observed in 19 of 61 patients (31.1%) treated with decitabine (evidence 2$^+$). Neutropenia and thrombocytopenia were the possible side effects with an expected incidence of 12% and 5%, respectively. A mortality rate due to drug toxicity of 7% was observed in the treated patients (evidence 2$^+$).

The EP agreed that the evidence was sufficient to provide recommendations on the use of decitabine or azacytidine and stated that:

- *patients with IPSS high risk disease, not candidates for hematopoietic stem cell transplantation or AML-like chemotherapy and aged less than 75 years should receive a course of decitabine or azacytidine (Recommendation level B);*
- *patients with clonal chromosomal abnormalities are highly recommended to receive a course of the drugs (Recommendation level B);*
- *a low- dose schedule (no greater than 335 mg/m^2 for azacytidine and 130 mg/m^2 for decitabine) is recommended (Recommendation level C).*
- *no specific recommendations on the use of one with respect to the other drug can be given.*

Which patients are candidates for immunosuppressive therapy?

Immune mechanisms have been implicated in the pathogenesis of marrow failure in MDS:[35] autoreactive T-cell clones were found to suppress hematopoiesis and the T-cell response is thought to be triggered by the pre-neoplastic clone and most likely to be directed against both MDS and residual normal hematopoiesis. Three immunosuppressive strategies have been tested in clinical trials: antithymocyte globulin (ATG), cyclosporin A (Cy-A) and high dose corticosteroids (HDC). The objectives of these therapies are first to attain a durable improvement of cytopenias and reduce red cell and platelet transfusions when necessary; however, extension of survival is an objective that can be reached. The evidence for the use of ATG is based on data abstraction and analysis of 5 studies with a total enrollment of 72 patients. The strongest evidence for an effect of ATG on cytopenias and survival was a phase II prospective trial first reported as a preliminary study in 25 transfusion-dependent MDS patients and later published in full concerning 61 patients (evidence 2$^+$).[36] Patients received ATG at a dose of 40 mg/kg/day for 4 days and were evaluated for 38 months (median). Thirty-three percent of the patients became transfusion-independent within 8 months of treatment (median 75 days); 56% severely thrombocytopenic patients had sustained platelet count increases, and 44% of the severely neutropenic patients achieved sustained neutrophil counts >1000/μL. In the subset of 41/61 patients with INT-1 IPSS risk score, responders had 100% survival at 3 years and no disease progression. These results can be compared with the 45% survival (p<0.0004) and 51% probability of disease progression in non-responders (p=0.02). The literature search for Cy-A therapy identified 3 case series (evidence 2$^-$) with a total enrollment of 36 patients. Thirty-four of the patients (94.4%) had RA and 18 (50%) had a hypoplastic bone marrow. The response rate ranged from 55% to 87% of the cases. The presence of HLA-DRB1-15 predicted the response to immunosuppression (evidence 2$^-$).

The literature search for HDC therapy identified 3 indexed case series (evidence 2$^-$) with a total enrollment of 56 patients. By excluding 27 patients who received HDC in association with other immunosuppressive treatments, of the 29 remaining patients, 23 (79.3%) had RA. A response (complete or partial) was obtained using 1000 mg high dose methylprednisolone × 3 days in 7 of the 23 patients with RA (30%) and in 0 out of 6 of those with the RAEB subtype.

The EP agreed that there was enough evidence to provide recommendations on the use of ATG and Cy-A. The EP stated that:

- *patients with a low- or INT-1 IPSS risk class, judged to require treatment and not candidates for hematopoietic stem cell transplantation or AML-like chemotherapy, should receive a course of ATG or Cy-A therapy (Recommendation level B);*
- *the use of ATG or Cy-A is highly recommended in the presence of a hypoplastic bone marrow or of the haplotype HLA-DRB1-15 (Recommendation level A);*
- *it is not possible, today, to give recommendations on the use of one of the different types of ATG (horse or rabbit), on the choice between Cy-A or ATG or on the use of any of the possible immunosuppressive drug combinations.*

Appropriateness of use of hematopoietic growth factors

Which patients are candidates for recombinant human erythropoietin?

To address the problem of hematopoietic dysfunction in MDS, experimental therapeutic approaches focused on the use of hematopoietic growth factors and biological response modifiers that could decrease the rate of apoptosis and enhance the differentiation of preleukemic progenitor cells or stimulate the growth of residual normal hematopoietic clones. Among the growth factors, recombinant human erythropoietin (rHuEPO) is the most widely used one. The rationale for treating MDS patients with rHuEPO is the possibility of overcoming the defective proliferation and maturation of the erythroid precursors by pharmacological doses of rHuEPO. There are literature reports on the use of rHuEPO both as a single agent and associated with other hematopoietic growth factors, such as GM-CSF, G-CSF or IL-3. The aim of these treatments is to raise the hemoglobin level or to reduce transfusion requirements, thus improving the patients' quality of life.

Evidence for the use of rHuEPO as a single agent is based on data abstraction and analysis of 28 studies. Two meta-analyses reviewed, respectively, 10 studies published before 1994 (evidence 1^-)[37] and 17 studies published before 1995 (evidence 1).[38] Two phase III randomized controlled trials evaluated the use of rHuEPO versus placebo (evidence $1^=$).[39,40] In the meta-analyses, overall response was 23.5% and 16.1%, respectively. A RA subtype and a serum erythropoietin lower than 250 mU/mL (or 200 mU/mL) were predictors of good response. The first randomized trial enrolled 20 patients with RA or RARS and treated them with a weekly dose between 1,600 and 3,200 U/kg/week, intravenously. A response occurred in 1/8 (12.5%) of the evaluable patients. The second trial enrolled 87 patients with a hemoglobin lower than 9 g/dL and bone marrow blasts lower than 10%. Patients received 150 U/kg/day subcutaneously for 8 weeks, and the response rate was 14/38, i.e. 36.8%, versus 4/37, i.e. 10.8% (p=0.007). RA, no need of transfusion and serum erythropoietin lower than 200 mU/mL were predictors of response.

Twenty four phase I-II clinical studies (evidence 2^+ in 4 and 2^- in 19) enrolled a total of 500 patients. Different inclusion criteria (low Hb level, transfusion dependence, low serum erythropoietin), different response criteria and different doses of the drug made the analysis of the results hard. Combining all the data and using the response criteria of the respective authors, an increase in hematocrit or a reduction of transfusion requirements was reported in 31% (range 0-76%) of the patients treated with rHuEPO. By applying a more stringent definition of response, i.e. discontinuation of transfusion requirements or an increase in hemoglobin concentrations of at least 1.5 g/dL, only 16% of the patients reached the target. In six phase I-II studies, a low level of serum erythropoietin predicted the response.

Recent communications envisaged the use of rHuEPO at very high doses, but no peer reviewed paper had been reported by the close of this systematic review.

Evidence for the use of rHuEPO associated with G-CSF is based on 8 studies. None made a comparison between rHuEPO alone and the association of rHuEPO plus the growth factor. In one randomized study,[41] G-CSF followed by G-CSF plus rHuEPO was compared to rHuEPO alone followed by the combination of the two growth factors. The whole response rate of rHuEPO associated with G-CSF was 38% without any statistical difference between the two different treatment groups. In six patients who did not respond to rHuEPO alone, a response to the association with G-CSF was attained. Seven clinical phase I-II studies evaluated the association of rHuEPO with G-CSF in a total of 197 patients (evidence 2^+ in 4 studies and 2^- in 3 studies). According to the authors' definition of response, a response was attained in 43% of the patients.

The EP agreed on the following:

- *patients with moderate to severe anemia (Hb lower than 10 g/dL) and refractory anemia or refractory anemia with ring sideroblasts, should have their serum erythropoietin level assayed. Those with serum EPO levels lower than 200 mU/mL should be considered for rHuEPO therapy (Recommendation level A);*
- *the doses to be used should be greater than 3×10,000 U/week (Recommendation level B);*
- *no recommendations can be given on the association of rHuEPO with other growth factors since the efficacy of associations needs to be supported by further evidence.*

Which patients are candidates for G-CSF or GM-CSF as a single agent?

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a cytokine that was identified through its ability to stimulate myeloid cells *in vitro*. The receptor for this growth factor has been found on the surfaces of cells belonging to all four hematopoietic cell lineages. In contrast to GM-CSF, granulocyte colony-stimulating factor (G-CSF) is a more lineage-restricted growth factor, which exerts

most of its effects on cells of the granulocyte lineage. The review of evidence on G-CSF and GM-CSF was based on data abstraction and analysis of one controlled trial, 8 non controlled trials and 7 series of a few cases. The randomized controlled trial (evidence 1^{++}), issued from the EORTC Leukemia Cooperative group,[42] compared the outcomes of managing neutropenia, anemia, thrombocytopenia and disease progression in patients with different severity scores and using two different daily doses of GM-CSF (either 108 mg or 216 mg/daily for 8 weeks) in 82 patients. Results showed that the drug increased circulating neutrophil counts in 66% of MDS patients. Improvements in other cell lines were less consistent. These results were not translated into increased patient survival rates. Data supporting the routine, long-term, continuous use of the growth factors are lacking. These observations were confirmed in a randomized trial that is available only in abstract form, and thus not considered in the review: overall survival was shorter in the G-CSF recipients and 22/81 treated patients developed thrombocytopenia (thrombocytes decreased during G-CSF administration to less than 50% of baseline values).[43] The effect of increased granulocyte counts on the frequency of infection is still unclear: the number of infections was reduced in one trial,[44] but in another one, some patients who had not suffered from any infection at the start of GM-CSF treatment developed infections during the treatment. Evidence translated from other diseases in which there is a tendency to develop febrile neutropenia consistently showed that the routine use of G-CSF or GM-CSF in previously untreated patients was not justified by the existing data.

The EP concluded that:

- *on the basis of the existing evidence, daily G-CSF or GM-CSF in MDS patients with the aim of improving the hematologic condition of the disease and slowing-down disease progression is not recommended (Recommendation level B);*
- *the use of the drug in severely neutropenic patients with documented infection is not recommended routinely, but must be decided on a case to case basis (Recommendation level D).*

Appropriateness of use of new therapies

The clinical and biological heterogeneity of MDS has suggested the possibility of multiple therapeutic targets. The EP agreed that a number of new drugs are worthy of note.

Topotecan. Topotecan, a topoisomerase I inhibitor, interacts with the enzyme topoisomerase I (topo I), and stabilizes the topo I-DNA complexes eventually leading to cell death. More topo I is present in tumor cells than in normal cell counterparts, which makes the enzyme a logical target for drugs that inhibit topo I. Evidence for the use of topotecan was based on data analysis of a phase I-II study (evidence 2^{+}) that enrolled 28 patients with high risk MDS. The complete remission rate in those patients was 36%, however, the median survival time was 10.5 months, and mortality during therapy induction was 20%.

Thalidomide. Thalidomide has an anti-TNF, anti-angiogenic and immunomodulating activity: all these effects are desirable in MDS patients. The evidence for the use of thalidomide is based on a phase I-II study (evidence 2^{+}) with a total enrollment of 73 high risk MDS patients.[45] The complete remission rate in those patients was zero, but 16 patients showed hematologic improvement and 10 previously transfusion-dependent patients became transfusion independent. Low risk patients had a better response.

Amifostine. Amifostine is a phosphorylated aminothiol that was found to promote the formation and survival of primitive hematopoietic progenitors derived from MDS bone marrow.[46] Oxidative stress has been demonstrated in MDS $CD34^{+}$ cells,[47] and could contribute to apoptotic cell death. Amifostine can act as an alternative substrate for reactive oxygen species and reduce the formation of DNA adducts.

The evidence for the use of amifostine was extracted from 11 studies (evidence 2^{-} to 3) with a total enrollment of 131 patients. Most patients were in a low or INT-1 risk class, but the administration regimens and hematologic responses were heterogeneous. No complete responses were attained and a partial response was obtained in a percentage of patients ranging from 0 to 66%. Further work in terms of drug scheduling and method of administration (subcutaneous versus intravenous) are necessary before recommending the drug.

Interleukin-3. Interleukin (IL)-3 is a multipotent hematopoietic growth factor produced by activated T-cells, monocytes/macrophages and stromal cells. The rationale for the clinical use of IL-3 in MDS is its capacity to stimulate multilineage hematopoietic response with an increase of neutrophils, platelets and hematocrit in patients with normal hematopoiesis. Evidence for use of IL-3 in MDS was extracted from 6 studies (evidence 2^{-} to 3) with a total enrollment of 85 patients. Besides an increase in absolute neutrophil counts in nearly half of the patients, platelet counts increased in a quarter of

them. However, IL-3 improved platelet counts mainly in patients with moderate thrombocytopenia (platelet count greater than 50×10^3/L)[48] and was associated with relatively important side effects at higher doses. The adverse effects of IL-3 mainly included fever, bone pain and headache. No trial compared the effects of IL-3 on hematopoiesis in the long-term and no trial compared these effects with those produced by other safer drugs such as danazol or G-CSF or GM-CSF. It appeared that future application of IL-3 in combination with other cytokines could be an attractive way forward in the prevention of treatment-related mortality and morbidity in MDS patients.

Retinoids. Studies explored the use of retinoids, but their results are difficult to interpret because of the differences in agents, doses and schedules and the use of additional agents. All-trans retinoid acid (ATRA) has been reported to have poor activity when used as a single agent.

The EP agreed that:

- *existing evidence on the use of topotecan, thalidomide, interleukin-3 and all-trans retinoic acid is too scanty to support any recommendations. The EP recommended that these agents should be used only in well-designed clinical trials.*

The optimal transfusion and iron chelation therapy

Red cell transfusion

In deciding whether to use red cell transfusion in MDS patients, the need for possibly improved oxygenation must be weighed against the risks of adverse consequences, both short-term and long-term. There are three general types of possible disadvantages: transmission of infection, adverse effects attributable to immune mechanisms and iron overload. In modern blood banking practice, bacterial contamination of red cell units is rare and human hepatitis viruses and HIV infection, after recent changes in criteria for donor acceptance and the introduction of specific laboratory tests, presently pose only a remote hazard. Cytomegalovirus infection occurs with moderate frequency among those recipients without prior infection. Most of these infections are asymptomatic except among immunocompromised patients.

Available evidence on the criteria for the use of red cell transfusion in MDS is scanty, thus general criteria issued for chronic disorders with anemia, such as thalassemia, may be adopted as translated evidence. The prevalent old age of the patients with MDS stresses that due attention must be given to symptoms of anemia rather than a fixed hemoglobin level as a criterion for transfusion. After general discussion, the EP pronounced as follows:

- *no single measure can replace good clinical judgment as the basis for decision-making regarding red cell transfusion;*
- *all patients with severe anemia (Hb lower than 8 g/dL) should receive red cell transfusion while transfusion is exceptionally indicated in patients with mild anemia (Hb greater than 10 g/dL) (Recommendation level D);*
- *standard red cell concentrate is the component to be utilized (Recommendation level D);*
- *when repeated non-hemolytic, febrile transfusion reactions occur, administration of leukocyte-reduced blood products to patients likely to require continuing transfusion support is indicated (Recommendation level D);*
- *in the stem cell transplant setting, leukocyte-reduced units may be utilized instead of CMV-negative donor derived units (Recommendation level D).*

Platelet transfusion

The increased use of platelet transfusions during the past 15 years has prevented most hemorrhagic deaths in hematologic disorders. Furthermore, this therapy has made it possible to treat patients with drugs that temporarily suppress platelet production. With this benefit, however, the problems are that transfused platelets can elicit an immune response in recipients, so that further transfusions are no longer effective. The prophylactic administration of platelets is controversial, and there is uncertainty as to the platelet levels that predispose thrombocytopenic patients to hemorrhage and as to the effectiveness of modalities other than platelets in the prevention of bleeding. Clinical decisions regarding platelet transfusion are hampered by an insufficient number of properly controlled trials, by imprecise methods of evaluating clinical need, and by uncertain methods for measuring effects. The platelet levels that predispose thrombocytopenic MDS patients to hemorrhage and the efficacy of therapeutic modalities other than transfusion are not well defined. Available evidence on the criteria for the use of platelet transfusions in MDS is scanty, thus general criteria issued for acute leukemia and lymphomas may be adopted as translated evidence. After general discussion, the EP stated the following:

- *the patient with severe thrombocytopenia may benefit from prophylactic administration of platelets. The value of 10,000 platelets/μL is the level of thrombocytopenia to be used to decide*

when to transfuse platelets prophylactically (Recommendation level D);
- *in patients with fever, infections, or a rapid platelet decrease, the level should be increased to 20,000 platelets/μL (Recommendation level D);*
- *many patients with chronic thrombocytopenia can be observed without prophylactic transfusion, reserving platelet transfusion for episodes of hemorrhage or during active treatment (Recommendation level D).*

Iron chelation

Dependency on regular blood transfusions can be a major clinical problem in MDS. Chronically transfused patients develop iron overload which in time becomes responsible for variable degrees of organ damage and dysfunction. Evidence on the efficacy of iron chelation therapy on iron overload of MDS patients is reported in 7 uncontrolled studies for a total of 29 patients (evidence from 2-- to 3): 23 were treated with desferrioxamine (DFO) and 6 were treated with the oral chelator deferipone (L1). Efficacy was studied by serum ferritin changes in 14 patients:[49] with a dose of 2 g/day DFO for 5 days per week or 30 mg/kg for 3 days per week, serum ferritin concentration decreased in 10/14 patients (71.4%), but increased in 2 and remained stable in one. Efficacy has been studied by MRI-determined liver iron concentration in 11 patients: liver iron concentration decreased in all patients with a dose of DFO of 2 g/die, but the reduction was only minor in five patients. In a prospective study, 5 patients with a median age of 63 were treated with subcutaneous bolus injection in two divided doses or a pump-driven slow infusion over 12 hours of 2 g of DFO diluted in 10 mL of distilled water. The iron excretion induced by bolus injection was not statistically different from that induced by subcutaneous infusion.

In only two patients with MDS was the long-term effect of iron chelation with L1 evaluated. The urinary iron excretion was greater than 25 mg/24h and this was sufficient to bring the patients to negative iron balance. However, there was no overall change of serum ferritin over the period of up to 15 months.[50] The efficacy of iron chelation in decreasing blood requirements was reported in 7 out of 11 (64%) patients published in two separate papers.[51] Thirty-six percent of the patients became blood transfusion independent after 18-26 months of treatment and were followed-up from 3 months to 3 years.

There are no studies in MDS which evaluate the relationship between the body iron burden and the clinical syndrome of iron overload and damage.

The EP agreed that iron chelation should be considered as a therapy for MDS and issued the following recommendations:

- *adult patients with MDS who have previously received more than 50 red blood cell units and for whom a life span longer than 6 months is expected should receive iron chelation therapy (Recommendation level B);*
- *desferrioxamine at the dose of 2 g daily by 12 hours subcutaneous infusion or 1 g daily by subcutaneous bolus for 5 days per week is recommended (Recommendation level C).*

Patient-related questions

What are the appropriate therapies in patients older than 75 years ?

In the absence of therapies that can prolong life without side effects, due to the high toxicity of chemotherapy in older patients, the EP agreed that abstaining from any cytotoxic therapy may be a rational way of managing older patients. In the absence of literature dealing with the problem, in particular of trials assessing low-dose chemotherapy, differentiating drugs or hypomethylating agents specifically in patients older than 75 years, the EP agreed that:

- *for older patients, i.e. those above 75 years old, the only appropriate therapy is transfusional therapy, recombinant human erythropoietin or danazol according to the specific recommendations (Recommendation level D).*

What are the approprate therapies in the patients younger than 18 years?

MDS are relatively unusual in childhood, representing only 5-7% of pediatric hematologic malignancies, although it has been suggested that up to 17% of pediatric myeloid leukemias (AML) may have had a previous myelodysplastic phase. MDS in children are characterized by an aggressive clinical course, the virtual absence of RARS and the presence of peculiar variants, such as JMML. These facts must be held in due consideration in the process of deciding the optimal therapeutic strategy. Moreover, on the basis of the long life expectancy of children, data available on the different treatment options, mainly referring to adult patients, are only partially applicable to the management of childhood MDS. The primary aim of a pediatric hematologist must be a definitive cure, achievable with the eradication or differentiation of the malignant clone, such as to reconstitute normal hematopoiesis.

No trial has specifically addressed the use of sup-

portive treatment, low-dose chemotherapy, hypomethylating agents or hematopoietic growth factors in children with MDS. As far as concerns the use of AML-like chemotherapy in children, a study published by the *Nordic Pediatric Haematology Group* compared the outcome of children with *de novo* MDS and children with *de novo* AML, and documented that patients belonging to the former group had a lower rate of complete remissions and a higher treatment-related mortality.[52] Few studies, the majority of which enrolled a limited number of patients, have specifically addressed the issue of the role of allografting in children with MDS and several crucial questions have still not been tackled by clinical studies. In particular, it has still not been precisely defined what percentage of children with MDS can be cured by an allograft and the optimal preparative regimen to be employed. Studies on the use of allografts in CJMML or in other hematologic disorders of childhood suggested that patients given a busulfan-based preparative regimen have an outcome comparable to or even better than that observed in patients given radiotherapy.

The expert panel's recommendations

- *all children with MDS and their siblings shoud be HLA typed in order to address the patients to allogeneic stem cell transplantation (Recommendation level B);*
- *in the absence of an HLA identical donor, an unrelated donor should be searched for (Recommendation level C);*
- *busulfan-containing conditioning regimens and a busulfan dose to reach plasma levels of 600-900 ng/mL are recommended (Recommendation level B);*
- *no recommendations can be given at present on the use of preconditioning AML-like chemotherapy in IPSS high risk patients.*

Disease management related questions

Where should a patient be managed?

In the absence of this question having been specifically addressed in the literature, the EP, after discussion, recommended that patients with a history, symptoms and laboratory findings suggestive of MDS should be referred to hematology departments or units for careful investigation and diagnosis, or, when hospitalized in long-term care institutions, should be investigated by the consultant hematologist. Patients being managed using supportive therapy, rHuEPO or danazol, which would not normally be planned to produce prolonged neutropenia, should be managed in a hematology unit or in a general medical ward under the care of a consultant hematologist. Patients requiring standard or high-dose chemotherapy regimens, such as those used in acute leukemia, should be admitted to hematology units where a number of single room facilities must be available.

Patients enrolled in programs of autologous stem cell transplantation or related allogeneic stem cell transplantation should be cared for in centers with a proven record in transplantation. This derives from the translated evidence from allogeneic bone marrow transplantation that suggested that the number of cases treated each year affects outcome, i.e. the greater the experience of the unit, the better the results.

What are the economic aspects involved in the treatment of MDS?

Hematopoietic growth factors, immunotherapy, chemotherapy and hematopoietic stem cell transplantation are expensive interventions, and their use in patients with MDS increases the cost of their management. On the other hand, the outcome of these interventions has the potential to improve both life expectancy and morbidity, thus improving the patient's quality of life, and all these are valuable outcomes that potentially compensate the cost. Patients whose anemia is improved by rHuEPO treatment are spared the risk of blood transfusion and its associated costs, which have been estimated to be $220-$400 per red cell unit. The cost of blood and its scarcity in most countries is sufficiently high to make rHuEPO therapy cost-effective in the group of patients that are transfusion-dependent and may be predicted to respond to therapy. Analysis of the cost/benefit ratio is more difficult in hematopoietic stem cell transplantation, chemotherapy and immunotherapy, because no monetary value has been assigned to the late benefits of improved disease course and freedom from disease-related morbidity. Analysis of the economic aspects of these issues awaits further data.

What are the quality of life aspects involved in the therapy of MDS?

Quality of life is significantly impaired in patients with advanced MDS. The assessment of quality of life impairment has so far focused only anemia, revealing a reduction from 3 to 12 point percent with respect to that in the general population. However, quality of life is relevant in patients undergoing chemotherapy and after hematopoietic stem cell transplantation for graft-versus-host disease, transplant complications and therapy. Since MDS therapy decisions are taken with marginal differences in

treatment results and risk-benefit profiles, balancing effects with outcomes also in terms of quality of life is mandatory. Considering that individual patients differ in the value they place on these issues, clear communication of benefits and risks is an essential component in enabling as informed a joint treatment decision as possible. Absolute and relative benefits and risks of therapy must be discussed openly.

What should the medical profession know about treatment of MDS, and what should be done to increase awareness?

Despite the accumulation of a substantial body of scientific information about MDS, large segments of the health professions remain relatively uninformed, or, even worse, misinformed, about much of what is known. This lack of information may result in patients being denied the benefits of an early diagnosis and of appropriate treatment for their disease. Improving professional knowledge about MDS will serve to remove those barriers and will foster more open communication and more effective treatment of this condition. First and foremost, information on MDS should be included in the core curricula of undergraduate and graduate professional schools. To increase practitioners' knowledge of this condition, the inclusion of presentations on MDS at scientific meetings of appropriate medical specialty associations, medical societies, and similar organizations of other health professions, should be encouraged. Continuing education courses focusing on the classification of MDS and appropriate diagnostic measures and treatment should be offered. Professionals most likely to provide care to people with MDS should be encouraged to attend these courses. Other special groups that are affected by MDS issues include pharmaceutical companies, and developers of technology. Funders of research, both public and private, must be involved in this developing field. Because MDS is a problem of great magnitude in long-term care settings, special emphasis should be placed on educating nurses aides.

What are the key research areas that will improve our knowledge about treatment of MDS?

During the past decade, major advances in the therapy of MDS have resulted from analyses of large prospective randomized trials. Worldwide, however, few MDS patients are entered in clinical trials. To achieve continued improvements in treatment, efforts should be made to improve patient and physician participation in these studies.

Randomized clinical trials evaluating the roles of high-dose chemotherapy need to be completed to determine whether these treatments have a role in the standard management of MDS. Additional studies are also needed to determine the importance of variations in the doses and schedules of the drugs used in chemotherapy regimens that are currently accepted as being standard. As yet unproven treatments that must be critically evaluated in prospective trials include thalidomide therapy, the value of combined growth factors with chemotherapy, and whether optimal immunosuppressive therapy is equivalent, superior, or additive to chemotherapy. The risks and benefits of low-dose conditioning regimens for allogeneic hematopoietic stem cell transplantation should also be examined.

Although treatment of MDS, in particular hematopoietic stem cell transplantation, has been found to produce significant improvements in survival, the ability to predict the value of these treatments in individual patients is limited. The development of accurate predictors of treatment efficacy would permit better targeting of treatments, improving efficacy and reducing the morbidity and cost of treatment. It is essential that the value of predictive and prognostic factors be evaluated using standardized protocols in well-designed clinical studies with sufficient statistical power to detect clinically important differences. Successful integration of new technologies, such as tissue and expression microarrays and proteomics, will depend on careful design and analysis of clinical investigations.

Quality of life is significantly impaired in patients with advanced MDS. Future research should characterize and validate quality-of-life tools in patients across gender and age. It will be important to identify effects of the disease and intervention on quality of life. Quality of life should be incorporated as an outcome in clinical trials evaluating disease risk and therapy. Interventions should be sought that will reduce side effects and improve quality of life. Decision aids and other techniques should be developed and evaluated for their ability to improve patients' involvement and understanding of treatment decisions.

Discussion

This study provides guidelines for clinical management of adults and children with MDS. The suggested recommendations are enlightened mostly by evidence: overall, 776 papers were retrieved from 1980 to 2001 in a systematic manner according to explicit criteria for quality and strength. Since meta-analyses or large randomized clinical trials, i.e. the

best techniques to compare specific therapies, are rare in MDS because the disease is uncommon, a large amount of evidence was derived from non-controlled, non-randomized trials in which subject selection and time-to-treatment biases precluded definite conclusions on the efficacy of therapies. Thus, the expert panel consensus methodology was required to complete the guidelines. Recursive partitioning then helped us to sort clinical scenarios into groups of similar appropriateness for the more relevant questions addressing appropriateness of when to start therapy, allogeneic stem cell transplantation and AML-like chemotherapy. The expert panel evaluated the therapies under three different perspectives: considering therapeutic strategies, patient presentations and community impact of the therapy. According to this methodology, evidence was judged sufficient to provide recommendations for a limited number of strategies: allogeneic and autologous stem cell transplantation, AML-like chemotherapy, low-dose chemotherapy, immunotherapy, use of growth factors and a few disease modifying agents, such as danazol and hypomethylating drugs.

Using a classification of evidence, the extent to which recommendations can be based on quality scientific evidence is low. Only four of the recommendations were supportable by level 1 scientific evidence. This finding reflects experience in most hematology-oncology disorders.[53] As a matter of fact, currently, practice guidelines can be based on high-quality scientific evidence only for initial decisions in newly diagnosed patients. However, the poor prognosis associated with relapsed or refractory disease without curable therapies continues to be managed on the basis of clinical skill and experience. This is reflected in our guidelines in which many of the recommendations were based on expert judgements consensus.

The results of these guidelines suggest that the critical determinant in planning therapeutic options in patients with MDS is the patient's age. However, considering that the patient's IPSS risk category improves outcome analysis, and that performance status has a major influence on the patient's ability to tolerate intensive therapies, these two issues also received strong consideration in the guidelines.

The EP agreed that it is important to stratify patients into age groups. In children (younger than 18 years), in which the primary aim is a definitive cure, stem cell transplantation or AML-like chemotherapy resulted the prime options for the eradication of the malignant clone and reconstitution of normal hematopoiesis. In older patients (older than 75 years), in the absence of therapies that can prolong life without severe side effects, the EP agreed on abstaining from giving cytotoxic therapy. In adult patients, 55 years of age was chosen as the age cut-off of eligibility for allogeneic stem cell transplantation in patients with intermediate or high risk IPSS categories, and 40 years of age in patients with low risk when presenting with moderate to severe anemia or with unfavorable cytogenetics. This is in agreement with most non-evidence-based suggestions, even though the recently produced guidelines by the *National Comprehensive Cancer Network*[54] recommended stem cell transplantation in patients younger than 60 years, while NCI guidelines,[55] stated that patients with *de novo* MDS should be addressed to allogeneic bone marrow transplantation when younger than 40 years. These different results stem from the fact that the evidence is sufficient to address patients to stem cell transplantation, but the issue of an age threshold for doing so is based on translated evidence and on the consensus of experts.

Sixty-five was the age of eligibility for AML-chemotherapy and was also indicated as the threshold age for a wait-and-see strategy, in association with IPSS risk class and severity of anemia. Besides the key therapeutic strategies, i.e. high-dose chemotherapy and allogenic bone marrow transplantation, possible therapeutic strategies are rare. Disease-modifying agents, such as danazol, immunotherapy or demethylating agents, were recommended in patients with a severe disease and who were not suitable for high dose-chemotherapy or allogeneic stem cell transplantation. A high number of new therapies were considered worthy of study, but the existing evidence did not allow their use in clinical practice to be recommended and the expert panel limited itself to urging well-designed clinical trials.

The panel expressed the view that a number of research issues are important in this disease. Carefully designed trials which incorporate quality of life issues and cost analyses should give complete information if evaluated according to established standard criteria for disease improvement and response. It is believed that the therapeutic recommendations issued in these guidelines will be greatly influenced by the large number of clinical trials that will be concluded in 2002 and 2003. The present guidelines should, therefore, be replaced by the end of 2003.

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All authors provided substantial contributions to conception and design, acquisition of evidence and analysis and interpretation of data, in particular dur-

ing panel meetings. All authors also participated in drafting the article and revising it critically, and gave final approval of the version to be published. GB, MM and LNL were responsible for the project's design and analysis of results. GB, MC and FL were responsible for manuscript preparation. All the authors critically revised the final version of the paper.

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Disclosures

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Last-minute addendum: literature review up to 31 July 2002.

The present guidelines were based on systematic review of literature published up to 31 July 2001; however, analysis of data published since that date up to 31 July 2002 was performed before publication of the paper. We found 45 new articles dealing with therapy of MDS. The randomized controlled trial undertaken in 191 patients with MDS to compare azacytidine (75 mg/m^2/day subcutaneously for 7 days every 28 days) with supportive care, and previously reported in abstract form,[34] was published *in extenso*.[56] Responses occurred in 60% of patients in the azacytidine arm compared with in 5% receiving supportive care. This study reinforces the recommendation of the guidelines about the use of hypomethylating agents. A multicenter phase II trial enrolled 118 anemic patients (Hb <10 g/dL with symptoms or transfusion-dependent anemia) older than 50 years and without prior cytotoxic therapy to receive rHuEPO therapy.[57] The overall response rate was 45.1% after 26 weeks of therapy. The response was higher in the good cytogenetic prognostic group, in patients with low blast count and with serum erythropoietin lower than 150U/L. The evidence of a delayed response to rHuEPO deserves that in the next update of the guidelines the expert panel considers recommendations about the duration of therapy before classifying a patient as a non-responder.

A clinical trial assessed the feasibility and efficacy of intensive remission-induction and consolidation chemotherapy followed by auto- or allo-SCT.[58] Relatively high remission rates were obtained that confirm the recommendation on the use of SCT. The study did not provide new information about whether this approach is better than treatment with chemotherapy only. In a multicenter retrospective study, the outcomes of 234 patients with MDS who underwent transplantation from HLA-identical siblings were analyzed according to the hematopoietic stem cell source used, that is, bone marrow or peripheral stem cells.[59] Use of peripheral stem cells reduced the median duration of neutropenia and thrombocytopenia. Two-year TRM was significantly reduced with peripheral stem cells, except for among patients who had either RA or high-risk cytogenetics, and the 2-year treatment failure incidence was significantly decreased (from 38% to 13%). This new paper reinforces the evidence for the use of peripheral stem cells in SCT recommended in these guidelines. Post-transplant outcomes of 510 unrelated bone marrow transplants were reported.[60] The 2-year cumulative incidence of treatment-related mortality was 54%. The other reports concerned non-controlled trials on the use of thalidomide, cyclosporin, amifostine, ATG, and danazol. The strength of evidence was in no case sufficient to question the validity of the recommendations of these guidelines.

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(A complete reference list file used for the systematic review can be requested to: marchettim@smatteo.pv.it)

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Manuscript processing

This manuscript was peer-reviewed by Professor Edoardo Ascari and by three external reviewers. The final decision to accept this paper for publication was taken jointly by Professor Ascari and two reviewers. Manuscript received June 18, 2002; accepted October 15, 2002.

Peer-review outcomes

The three reviewers were: Theo de Witte (Nijmegen), Arnold Ganser (Hannover) and Guillermo Sanz (Valencia). Peer reviewers were masked to author identity in order to avoid any bias and with the aim of improving both quality and fairness of reviews. All reviewers suggested major and/or minor changes and re-evaluated the revised manuscript. This latter was fully approved by Arnold Ganser and Guillermo Sanz. By contrast, Theo de Witte still disagreed with the authors on the following two points: a) omission of RAEB-t from myelodysplastic syndromes: Dr. de Witte suggested including this condition due to the difficulty in clearly separating it from RAEB; b) chemotherapy before allogeneic stem cell transplantation: the authors recommend not administering AML-like chemotherapy before transplantation to those patients who could be candidates for chemotherapy treatment, whereas Dr. de Witte believes that this is in contrast to the current policy in Europe.

Edoardo Ascari, Associate Editor
(Pavia, Italy)