Background

The Italian and British Societies of Hematology formulated evidence-based guidelines for the therapy of myelodysplastic syndromes (MDS).[1, 2] The need for updated and widely recognized therapeutic recommendations is perceived. The effort of developing and implementing evidence-based European guidelines is expected to result in optimizing the management of patients with MDS, and in attaining an ideal framework for clinical and translational studies.

Aim of the project

The aim of this work is to develop evidence- and consensus-based guidelines providing clinical practice recommendations that can support the appropriate choice of therapeutic interventions in adult patients with primary MDS.

Design and Methods

The development of the guidelines is a multistep process, consisting in:
1. Selection of an Expert Panel;
2. Systematic review of the literature and synthesis of evidence;
3. Key questions and list of indications;
4. Scenario analysis;
5. Formulation of recommendations.

1. Selection of an Expert Panel

An Expert Panel has been selected by the Coordinators of the Project (M. Cazzola, D. Bowen), according to the framework elements of the NIH Consensus Development Program.[3]

The Panel and the specific duties are as follow:

Expert Panel	*Affiliation*	*Specific topic*
Theo de Witte	University Medical Center Nijmegen, The Netherlands	Allogeneic transplantation
Guillermo F. Sanz	Hospital Universitario La Fe, Valencia, Spain.	Autologous transplantation
Ghulam Mufti	King's College Hospital, London, UK.	Intensive chemotherapy
David Bowen	Leeds General Infirmary, Leeds, UK	Low dose chemotherapy
Pierre Fenaux	Hopital Avicenne/Paris 13 University, Bobigny, France	Hypomethylating agents
Eva Hellström-Lindberg	Karolinska University Hospital, Stockholm, Sweden	Growth factors
Jaroslav Cermak	Institute of Hematology, Prague, Czech Republic	Immunosuppressive therapy
Mario Cazzola	University of Pavia, Policlinico S. Matteo, Pavia, Italy	Management of anemia
Norbert Gattermann	Heinrich-Heine University Hospital, Dusseldorf, Germany	Management of iron overload
Consuelo del Cañizo	University Hospital, Salamanca, Spain.	Management of thrombocytopenia

2. Systematic review of the literature and synthesis of evidence

A systematic review of the literature has been performed (by Luca Malcovati and Matteo Giovanni Della Porta) according to the following criteria:
•English language;
•Year of publication: 1985-2005;
•Studies including 10 patients or more;
•Source: PubMed; proceedings ASH, ASCO, EHA, MDS international meeting 2003-2005;

The level of evidence and the grades of recommendations were rated according to the Revised Grading System for Recommendations in Evidence Based Guidelines of the Scottish Intercollegiate Guidelines network Grading Review Group.[4]

Levels of evidence

1++	High quality meta-analyses, systematic reviews of randomized clinical trials (RCTs), or RCTs with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews or RCTs, or RCTs with a high risk of bias
2++	High quality systematic reviews of case-control or cohort studies *or* High quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal
2+	Well conducted case-control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
2-	Case-control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion

Grades of recommendations

A	At least one meta-analysis, systematic review, or RCT rated as 1++ and directly applicable to the target population *or* a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results *or* extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results *or* extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4 *or* extrapolated evidence from studies rated as 2+

3. Key questions and list of indications

A list of key clinical questions will be formulated based on the major issues emerged from the first panel meeting held in Madrid on October 26-27, 2005. The questions will point to the possible and recommendable strategies within each therapeutic category, to the possible and optimal candidates, and to the risks deriving from the therapy.
Then, the Expert Panel will be invited to formulate in an independent manner proper evidence-based statements for each question. This will be realized through a web site with a restricted access for each panelist.
Basing on the statements of the experts for each question, the clinical variables will be defined that have to be taken into account in deciding whether to recommend a particular procedure (list of indications), and recommendations will be formulated and ranked according to the supporting level of evidence.

4. *Scenario analysis*

Scenario analysis will be used to reach a consensus, besides the frontiers of evidence. A series of clinical scenarios will be defined basing on the parameters relevant to therapy choice. For each clinical scenario the members of the Expert Panel will be asked to rate the appropriateness of providing a certain treatment.
A procedure or treatment is considered to be appropriate if “the expected health benefit (e.g., increased life expectancy, relief of pain, reduction in anxiety, improved functional capacity) exceeds the expected negative consequences (e.g., mortality, morbidity, anxiety, pain, time lost from work) by a sufficiently wide margin that the procedure is worth doing, exclusive of cost.”[5]

Appropriateness will be scored according to a scale from 1 to 9 (1 indicates that the questioned strategy is totally inappropriate, and 9 that it is totally appropriate).
An appropriateness analysis will be carried out (median, dispersion of ratings) and levels of appropriateness will be defined as follow:
- Appropriate: panel median 7-9, without disagreement;
- Uncertain: panel median 4-6 or any median with disagreement (a disagreement is defined when considering all nine ratings, at least one is a 1, and at least one is a 9);
- Inappropriate: panel median of 1-3, without disagreement.

5. Formulation of recommendations

Basing on evidence from the literature, question-specific statements and scenario analysis final recommendations will be formulated. A final consensus conference could be hold at convenience of the coordinators and the panelists with the aim of reaching a definite consensus on question-specific statements and to agree on the appropriateness of some selected scenarios by means of nominal group technique.

References

1. Alessandrino EP, Amadori S, Barosi G, Cazzola M, Grossi A, Liberato LN, et al. Evidence- and consensus-based practice guidelines for the therapy of primary myelodysplastic syndromes. A statement from the Italian Society of Hematology. Haematologica 2002; 87: 1286-1306.

2. Bowen D, Culligan D, Jowitt S, Kelsey S, Mufti G, Oscier D, et al. Guidelines for the diagnosis and therapy of adult myelodysplastic syndromes. Br J Haematol 2003; 120: 187-200.

3. The National Insitute of Health (NIH) Consensus Development Program (CDP). http://consensus.nih.gov.

4. Harbour R and Miller J. A new system for grading recommendations in evidence based guidelines. Bmj 2001; 323: 334-336.

5. Brook RH, Chassin MR, Fink A, Solomon DH, Kosecoff J and Park RE. A method for the detailed assessment of the appropriateness of medical technologies. Int J Technol Assess Health Care 1986; 2: 53-63.