

athies and multiple myeloma, and malignant lymphomas. Moreover the Societies will provide regularly, twice a year, a list of medical and scientific events, including meetings, seminars, stages, and workshops, which have been selected for their quality, are worthy of the auspices of the Societies and can provide qualified credits for CME. Operating in this way at a national level will allow Italy to be ready to contribute to CME at the European level.

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## Practice guidelines for the therapy of primary myelodysplastic syndromes: a note of caution about their translation into clinical practice

Haematologica welcomes *Decision Making and Problem Solving* articles that report meta-analyses, rational approaches to diagnosis and treatment of specific disorders and, in particular, guidelines.<sup>1-4</sup> This issue reports the Italian Society of Hematology guidelines for the therapy of primary myelodysplastic syndromes (MDS),<sup>5</sup> a group of disorders that represent a therapeutic challenge.<sup>6-12</sup>

As underlined by Kassirer and Campion,<sup>13</sup> one of the major duties of biomedical journal is to help people who are not expert to decide what to believe and accordingly translate into clinical practice. The Italian Society of Hematology guidelines include a number of recommendations based on evidence and expert consensus. These recommendations, however, do not necessarily agree with the current approved indications for the use of the drugs and procedures concerned. Furthermore, they may disagree with recommendations by other expert panels.

In the case of myelodysplastic syndromes, the therapeutic option that best illustrates the current uncertainty is the use of recombinant human erythropoietin (rHuEpo) in the treatment of anemic MDS patients. The Italian Society of Hematology expert panel agreed on the following points:

a) 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 erythropoietin levels lower than 200 mU/mL should be considered for rHuEpo therapy (recommendation level A);  
b) the doses to be used should be greater than 30,000 U/week (recommendation level B).

Basically, there is only one well-designed, placebo-controlled, randomized trial that supports the use of rHuEpo in patients with anemia associated with low-risk myelodysplastic syndrome.<sup>14</sup> The recent ASCO/ASH guidelines on the use of rHuEpo patients with cancer<sup>15</sup> emphasize that the results of this study are limited in terms of generalizability because the definition of hematologic response was not standard. In addition there is no well-designed study that provides valuable information on maintenance of response by initially responsive MDS patients. Furthermore, the risk of rHuEpo-associated pure red cell aplasia<sup>16</sup> should now be taken into account in any treatment lasting more than three months in patients who are not given immunosuppressive therapy concomitantly. Last but not least, rHuEpo doses greater than 30,000 U/week for months or years involve extremely high costs, especially considering that only a portion of treated MDS patients show a definite response. So far, rHuEpo has not been approved by EMEA or by FDA for treatment of MDS. In Italy, it can be used under particular conditions, which include keeping patients' records and regularly providing the Ministry of Health *ad hoc* office with them.

In summary and more generally, how should the practising physician translate the above guidelines into clinical practice? There will be no substantial problem with the vast majority of MDS patients who are candidates to supportive therapy only. On the other hand, the minority of MDS patients who can benefit from allogeneic stem cell transplantation or intensive chemotherapy — the only two treatments that can prolong survival<sup>6</sup> — will be referred to appropriate hematology centers. Because of the inadequacies or uncertainties of the remaining treatment modalities, my personal recommendation is to implement the above guidelines following approval of the local institutional committee on human experimentation. An alternative solution would be to enroll the individual patient into a prospective clinical trial. Participation of MDS patients in clinical trials is strongly encouraged in order to improve our understanding of these disorders. Finally, to make the guidelines for the therapy of primary myelodysplastic syn-

dromes easier to use by the practicing physician, *Haematologica* is creating an online interactive decision pathway that will be available to our subscribers early in 2003.

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## References

1. Fabris F, Luzzatto G, Stefani PM, Girolami B, Cella G, Girolami A. Heparin-induced thrombocytopenia. *Haematologica* 2000; 85:72-81.
2. Burgio GR, Locatelli F. Alternative therapies and the Di Bella affair in pediatrics. A questionnaire submitted to Italian pediatric oncologists and hematologists. *Haematologica* 2000; 85:189-94.
3. Rock G, Porta C, Bobbio-Pallavicini E. Thrombotic thrombocytopenic purpura treatment in year 2000. *Haematologica* 2000; 85:410-9.
4. Dini G, Cancedda R, Locatelli F, Bosi A, Bandini G, Alessandrino EP, et al. Unrelated donor marrow transplantation: an update of the experience of the Italian Bone Marrow Group (GITMO). *Haematologica* 2001; 86:451-6.
5. 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; 87:1286-306.
6. Cazzola M, Anderson JE, Ganser A, Hellstrom-Lindberg E. A patient-oriented approach to treatment of myelodysplastic syndromes. *Haematologica* 1998; 83:910-35.
7. Grossi A, Fabbri A, Santini V, Leoni F, Nozzoli C, Longo G, et al. Amifostine in the treatment of low-risk myelodysplastic syndromes. *Haematologica* 2000; 85:367-71.
8. Musto P, Sanpaolo G, D'Arena G, Scalzulli PR, Matera R, Falcone A, et al. Adding growth factors or interleukin-3 to erythropoietin has limited effects on anemia of transfusion-dependent patients with myelodysplastic syndromes unresponsive to erythropoietin alone. *Haematologica* 2001; 86:44-51.
9. Ferrara F, Morabito F, Latagliata R, Martino B, Annunziata M, Oliva E, et al. Aggressive salvage treatment is not appropriate for the majority of elderly patients with acute myeloid leukemia relapsed from first complete remission. *Haematologica* 2001; 86:814-20.
10. Bernasconi C. Evidence-based approach to treatment of myelodysplastic syndromes. *Haematologica* 2001; 86:897-9.
11. Alessandrino EP, Amadori S, Cazzola M, Locatelli F, Mecucci C, Morra E, et al. Myelodysplastic syndromes: recent advances. *Haematologica* 2001; 86:1124-57.
12. Petti MC, Latagliata R, Breccia M, Alimena G, Spadea A, D'Andrea M, et al. Spontaneous remission in adult patients with de novo myelodysplastic syndrome: a possible event. *Haematologica* 2001; 86:1277-80.
13. Kassirer JP, Campion EW. Peer review. Crude and understudied, but indispensable. *JAMA* 1994; 272:96-7.
14. Anonymous. A randomized double-blind placebo-controlled study with subcutaneous recombinant human erythropoietin in patients with low-risk myelodysplastic syndromes. Italian Cooperative Study Group for rHuEpo in Myelodysplastic Syndromes. *Br J Haematol* 1998; 103:1070-4.
15. Rizzo JD, Lichtin AE, Woolf SH, Seidenfeld J, Bennett CL, Cella D, et al. Use of epoetin in patients with cancer: evidence-based clinical practice guidelines of the American Society of Clinical Oncology and the American Society of Hematology. *J Clin Oncol* 2002; 20:4083-107.
16. Casadevall N, Nataf J, Viron B, Kolta A, Kiladjian JJ, Martin-Dupont P, et al. Pure red-cell aplasia and antierythropoietin antibodies in patients treated with recombinant erythropoietin. *N Engl J Med* 2002; 346:469-75.