High-dose recombinant human erythropoietin for "low-risk" myelodysplastic patients: is more better?

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In present issue of the Journal Azzarà and Colleagues describe a retrospective series of 133 anemic patients with low/intermediate-1 risk myelodysplastic syndromes (MDS) treated with high-dose (40,000 IU twice a week) of alpha recombinant human erythropoietin (alpha-rHuEPO) (1).

According to the revised IWG criteria (2), the response-rate was 75%, 66% and 59% after 8, 16 and 24 weeks respectively. The erythroid response-rate was stratified according to both the International Prognostic Scoring System (IPSS) (3) and the WHO-based Prognostic Scoring System (WPSS) (4), and showed better response-rates in patients with a lower score, confirming a large series of previous trials who clearly show that in this clinical setting the lower is the risk-score of treated MDS patients the higher is the probability to obtain a positive response to a challenge with an erythropoiesis stimulating agent (EPO and darbepoetin) (ESA).

Alpha-HuEPO has been utilised for correction of anemia in MDS patients since more than twenty years, soon after human recombinant EPO became available in clinics for renal failure patients; the first studies performed in the early Ninety showed a disappointing overall response-rate which was observed in no more than 15% of MDS patients as a whole (5). These results were obtained using different but usually "standard" doses of alpha-rHuEPO in very different subsets of MDS patients; early trials enrolled in fact a relevant percentage of patients with advanced MDS, including subjects with refractory anemia with excess of blasts and/or patients with heavier transfusional need, and most of these patients would be in present days classified as "high-risk".

In the late Ninety a first score for predicting erythroid response to EPO was proposed, which introduced the idea that a better selection of MDS patients would increase the probability of a successful treatment (6).

When a first selection of MDS patients was performed, including only "low-risk" MDS anemic patients (clinically defined, before the publication of IPSS, as anemic MDS subjects with a blast count of less than 10%) the response-rate to alpha-rHuEPO was actually more than doubled (7).

In this new scenario, when only IPSS low or intermediate risk MDS patients have been included into the studies, the proportion of MDS anemic patients responding to ESA has significantly increased in the last decade.

A large meta-analysis by Moyo *et al*. pooled data from 30 rigorously selected studies (of 79 published) treating MDS patients with ESA at different dosing. The pooled erythroid response rate was 43.9% (8). A comparison between erythropoietin and darbepoetin showed no statistically significant difference when the erythroid response rate was compared between the two agents at corresponding dosing regimens, while higher dosing regimens of both alpha-rHuEPO- (60,000-80,000 U/wk) and darbepoetin (300 g/wk) yielded greater erythroid responses (50-71%) in lower-risk MDS, as shown in present paper by Azzarà *et al*. (1).

Nevertheless, it has to be noticed that in the studies utilising standard doses of ESA analysed in this meta-analysis the proportion of patients enrolled with more advanced disease was significantly higher; on the other hand, when strictly selected patients with lower-risk MDS have been challenged with standard doses of rHEPO, response-rates are very similar to what observed with higher doses (9) indicating that a truly low prognostic score (i.e., <1 for both IPSS and particularly a low WPSS) seems to be more relevant that the dosage of rHuEPO in order to predict the possibility to achieve a favorable erythroid

response in a given anemic patient with MDS.

It might be therefore difficult to understand if the improved therapeutic results shown in the more recent trials using higher doses of rHEPO are due to the increased dosage of rHEPO or to more selective inclusion criteria; it has also to be considered that in this clinical setting the standard doses of rHEPO used are nevertheless still pharmacological, largely exceeding the doses usually employed for the correction of anemia due to chronic renal failure.

Because the relatively high costs of treatment with rHEPO and its potential prolonged use in responding individuals with lower-risk MDS, the fact that even standard doses of EPO are effective as higher doses is important in order to restrain the costs of the treatment. Actually, all lower-risk MDS anemic patients are at present strongly recommended to be challenged with rHEPO or another ESA, and optimising the schedule of treatment might allow for a consistent saving of economic costs; furthermore, the use of the lowest effective dose of ESAs, as well as its discontinuation when appropriate (in particular when a responding patient does not respond to the treatment anymore) is extremely important not only for economical but also perhaps for safety reasons (i.e., ad example, the incidence of uncontrolled arterial hypertension or the incidence of thrombotic events).

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References

1. Azzarà A, Carulli G, Galimberti S, et al. High-dose (40,000 IU twice/week) alpha recombinant human erythropoietin as single agent in low/intermediate risk myelodysplastic syndromes: a retrospective investigation on 133 patients treated in a single institution. Am J Hematol 2011;86:762-7.
2. Cheson BD, Greenberg PL, Bennett JM, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood 2006;108:419-25.
3. Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood 1997;89:2079-88.
4. Malcovati L, Germing U, Kuendgen A, et al. Time-dependent prognostic scoring system for predicting survival and leukemic evolution in myelodysplastic syndromes. J Clin Oncol 2007;25:3503-10.
5. Hellström-Lindberg E. Efficacy of erythropoietin in the myelodysplastic syndromes: a meta-analysis of 205 patients from 17 studies. Br J Haematol 1995;89:67-71.
6. Hellström-Lindberg E, Negrin R, Stein R, et al. Erythroid response to treatment with G-CSF plus erythropoietin for the anaemia of patients with myelodysplastic syndromes: proposal for a predictive model. Br J Haematol 1997;99:344-51.
7. Italian Cooperative Study Group for rHuEpo in Myelodysplastic Syndromes, Ferrini PR, Grossi A, et al. A randomized double-blind placebo-controlled study with subcutaneous recombinant human erythropoietin in patients with low-risk myelodysplastic syndromes. Br J Haematol 1998;103:1070-4.
8. Moyo V, Lefebvre P, Duh MS, et al. Erythropoiesis-stimulating agents in the treatment of anemia in myelodysplastic syndromes: a meta-analysis. Ann Hematol 2008;87:527-36.
9. Balleari E, Clavio M, Arboscello E, et al. Weekly standard doses of rh-EPO are highly effective for the treatment of anemic patients with low-intermediate 1 risk myelodysplastic syndromes. Leuk Res 2011;35:1472-6.

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