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rHuEpo for the treatment of anemia in myelofibrosis with myeloid metaplasia. Experience in 6 patients and meta-analytical approach

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Abstract

Background and Objective. **Experience with recombinant human erythropoietin (rHuEPO) in the treatment of the anemia secondary to myelofibrosis with myeloid metaplasia (MMM) is slight up to now. We present our results of the treatment of 6 patients and a review of the literature in search of possible parameters predicting response to this treatment.**

Design and Methods. **From January 1994 to June 1996 all transfusion-dependent patients with MMM diagnosed in our hospital were included in this study. We established a minimum period of 4 weeks of treatment and a maximum of 12 if no response was observed. Initial dosages used were 100 U/kg s.c. 3 times weekly, increasing by 50 U/kg every 4 weeks where no response was observed. Response was defined as a reduction ≥ 30% of the previous transfusional needs. The review of the literature was made using a MEDLINE© search (January 1990-December 1996) on the keywords erythropoietin, myelofibrosis, and agnogenic myeloid metaplasia. A statistical study was made in search of possible parameters to predict response. The parameters studied include age, sex, hemoglobin, serum erythropoietin (sEPO) levels, transfusional dependency, transfusional requirements per month prior to treatment, maximum dosages used and dosage at which response was obtained.**

Results. **Only 2 of our 6 patients responded, both at a dosage of 600 U/kg/week (200 U/kg 3 times weekly s.c.). In addition to our 6 patients we have found only 28 other patients in the literature. For statistical calculation 2 of our patients were not considered as they did not complete the period of study. The overall rate of response was 17/32 (53.1%). In the univariate analysis comparing responders and non-responders we found a tendency to significance with respect to sex (p=0.07), sEPO (p=0.07) and transfusional needs in units of packed red blood cells per month (PRBC/m) (p=0.13). In this way patients with low sEPO, females and those with low transfusional needs (< 3 PRBC/m) respond better. This better response in females could be explained by the fact that their disease situation was more stable (with both lower sEPO levels and transfusional dependency). The best cut-off point in the sEPO to predict response was 123 mU/mL. No important side-effects have been observed except three cases of aggravation of splenomegaly. In two cases this condition improved when the rHuEPO was discontinued. The association of rHuEPO with hydroxyurea or interferon does not seem to affect the response.**

Interpretation and Conclusions. **Though the number of patients is low, our data suggest that some MMM patients, in particular females and individuals with low sEPO levels and with low transfusional needs, might benefit from rHuEPO in terms of elevation of hemoglobin levels. Unfortunately, transfusion dependent-patients, i.e. those in whom a beneficial effect of rHuEPO would be most welcome, are unlikely to respond, and more generally, treatment is not cost effective in medically responsive patients.**

Key words: erythropoietin, myeloproliferative disorders, myelofibrosis, agnogenic myeloid metaplasia, predictive factors

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Recombinant human erythropoietin (rHuEPO) has been used with moderate success in the treatment of anemia secondary to some pathologies involving the stem cell, such as myelodysplastic syndromes (MDS),[1] chronic myelogenous leukemia[2] or paroxysmal nocturnal hemoglobinuria.[3] Myelofibrosis with myeloid metaplasia (MMM) is a process affecting the stem cell that frequently produces anemia as well. In its treatment, among other drugs, androgens[4] or hydroxyurea (HU)[5] have occasionally been used but supportive therapy remains essential to maintain an acceptable quality of life in these patients. The use of rHuEPO in MMM has been very limited and experience with this drug is still slight. We present our results of the treatment of 6 patients with MMM, three of whom have been previously reported as showing no response.[6] A review of the literature has also been made in order to establish the possible parameters that could help to select those patients who could benefit from this therapy.

Materials and Methods

Patients

From January 1994 to June 1996 all transfusion dependent patients with MMM diagnosed in our Hospital were included in this study. Criteria for diagnosis included marrow fibrosis, splenomegaly and a leukoerythroblastic blood picture.[7] The trial could not be approved by the Ethical Committee of our Institution as the Committee did not exist at the beginning of the trial (it was formed in March 1996). However, informed consent was obtained from all patients. Transfusion dependency was the only criterion considered for inclusion in the study. From each patient data on age, sex, period of time since diagnosis, transfusional period, and other concomitant treatments were compiled as well as data regarding basal (prior to rHuEPO treatment) hemoglobin (Hb), leukocytes, platelets, reticulocytes, erythroblasts, ferritin, basal serum erythropoietin (sEPO), degree of transfusional dependency in units of packed red blood cell per month (PRBC/m) and size of the spleen before and after treatment. Basal Hb was calculated as the mean of the Hb levels before transfusion in the three months prior to treatment. PRBC/m was calculated as the mean of the transfusion requirements in the same period of time. Hb and PRBC/m post-treatment were obtained as the mean of their values after the beginning of treatment. Adverse effects during the period of study were also recorded if present. We established a minimum period of 4 weeks of treatment and a maximum of 12 if no response was observed. Initial dosages used were 100 U/kg s.c. 3 times weekly, increasing by 50 U/kg every 4 weeks if there was no response. This was defined as a reduction of at least 30% of the previous transfusional needs.

Selection of papers

The review of the literature was made using a MEDLINE© search (January 1990-December 1996) on the keywords erythropoietin, myelofibrosis, and agnogenic myeloid metaplasia. Those papers found were used as a source of new papers to include more patients (Table 1). We accepted the response criteria indicated in each study since differences were slight. These response criteria were variable, and in one study several could be considered, but they can be divided into 2 groups: ≥ 1 g/dL increase in the Hb levels, and ≥ 30% reduction in the degree of transfusion dependency. In order to compare the dosages used all were transformed into units/kg/week; if the data referring to sex, age, Hb, PRBC/m, sEPO, and dosage at which response was obtained were not clearly expressed they were not considered in the statistical analysis.

Statistical methods

Continuous parameters were described in terms of mean values (range). Categories were compared with Fisher's exact test and quantitative parameters with the Mann-Whitney U-test. ROC curves were used to calculate the best sEPO cut-off point to predict response. The expression "*n=*" indicates the number of patients available for each calculation.

Table 1. Articles included in the review of the literature. Results and maximum dosages used.

Year	*Authors*	*Response/ patients*	*Dosage° (U/kg/week)*
1990	Frutchman et al.	2/2	300 s.c.
1991	Iki et al.	0/1	15,000 i.v.*
1992	Cazzola et al.	1/3	750 s.c.
1992	Mittelman et al.	1/1	Not indicated s.c.
1992	Rafanelli et al.	1/1	1,050 s.c.*
1993	Aloe Spiriti et al.	4/7	800 s.c.
1993	Mohr et al.	0/2	1,680 s.c.
1993	Ziegler et al.	1/1	1,500 i.v.
1994	Tefferi et al.	0/4	450-900 s.c.
1994	Falkson et al.	2/3	Not indicated s.c.
1996	Bourantas et al.	3/3	600 s.c.*

*°Maximum dosage used; *fixed rHuEPO doses.*

Results

Results in our patients

From January 1994 to June 1996, six patients were included in the study. Table 2 shows epidemiological data of the patients as well as clinical and analytical parameters pre- and post-treatment with rHuEPO. Patient #1 was in the terminal stage and HU (500 mg every other day) was used during the last month of treatment together with rHuEPO; initial dosage was not modified due to his clinical situation and he died 2 months after beginning treatment due to progression of his disease. Patient #2 was initially considered as unclassified MDS (because no splenomegaly and a clear leukoerythroblastic blood picture was observed) evolving to MMM with progressive anemia. This case was reviewed later (prior to treatment) and the possibility of MDS was ruled out. He died 5 weeks after beginning treatment due to cardiac failure (this patient had previously suffered cardiopathy) but a rapid progression of the disease was observed during this period. Patient #3, in the terminal stage (as was patient #1) began HU (500 mg every other day) one month before beginning treatment with rHuEPO and this was maintained during the entire period of treatment. Patient #4 was treated for 9 months with 200 U/kg without requiring transfusional support; after this period she became newly transfusion-dependent (2 PRBC/m, the same amount as prior to rHuEPO treatment) and treatment was discontinued. She died

Table 2. Epidemiological, clinical and analytical data of our patients pre- and post-treatment with rHuEPO.

	*Patient #1**	*Patient #2**	*Patient #3*	*Patient #4*	*Patient #5*	*Patient #6*
Sex	Male	Male	Male	Female	Female	Male
Age	67	80	57	80	73	70
Response	NO	NO	NO	YES	YES	NO
T. Diagnosis (months)	10	6	17	96	15	2
T. Transf. dep. (months)	8	1	17	2	15	2
Initial dosage (U/kg)	100	100	100	100	100	100
Maximum dosage (U/kg)	100	150	200	200	200	200
Hb (g/dL)	8.9/10.6	10.5/9.3	6.7/6.8	8.7/9.9	9.7/10.3	9.1/9.7
Transfusion (PRBC/m)	8.3/9.5	3.6/8	10/10	2/0	2/1	7/6
sEPO (mU/mL)	17/56	26/NA	826/1507	16/4	123/233	510/512
Reticulocytes (%)	0.5/0.1	3.6/0.4	1.3/0.8	2.2/3	1.3/1.4	0.6/0.1
Erythroblasts^	1/0	2/0	5/4	6/21	2/0	0/0
Ferritin (ng/mL)	1620/2430	272/NA	2780/2850	738/1740	2230/1380	738/1840
Leukocytes ($\times 10^9$/L)	5.8/6.4	13.4/11.9	35/15	9.9/7.9	6.4/7	13.4/14.7
Platelets ($\times 10^9$/L)	333/291	109/204	20/15	164/181	189/231	222/216
Splenomegaly (cm)	15/25	5/5	10/12	9/9	3/0	5/8
Treatment (weeks)	8	5	12	12	12	12
Other treatment	HU	No	HU	No	No	No

*Patients #1, 2 and 3 were previously reported (ref. #6). *Not included in statistical study as the period of study was not completed; T. Diagnosis = Time since diagnosis; T. Transf. dep.= Time with transfusional dependency; Hb= Hemoglobin; PRBC/m = units of packed red blood cells/month; sEPO = serum erythropoietin; ^Over 100 leukocytes; HU= hydroxyurea.*

2 months later at home (cause unknown). In patient #5 treatment was maintained at a dosage of 200 U/kg after the period of study as her transfusional needs were reduced by 50% in this period and she became transfusion-independent one month later. She is still on treatment (subsequent follow up 6 months without transfusions). Patient #6 did not show any response to treatment and this was discontinued.

No effect on the other hematological series was observed except in patient #2 in whom the platelet count doubled. Only in patient #1 was an aggravation of the splenomegaly observed. No other adverse effects due to the treatment were observed during administration.

Results from the literature and our patients

A total of 28 other patients was compiled from 11 articles.[8-18] We made a statistical analysis of the data from all the patients. Data from 32 patients were analyzed. Patients #1 and #2 in our series were excluded as they did not complete the period of study proposed. With respect to sex (n=24) 16 were males and 8 females, mean age (n=29) 64.3 years (22-80). Mean values of the parameters analyzed were: basal Hb (n=24) 8.1 g/dL (5.4-12); basal sEPO (n=15) 573.5 mU/mL (7.9-2,281); seven patients did not require transfusions and of those who were transfusion-dependent, transfusional requirements were (n=15) 4.2 PRBC/m (2-12); maximum dosage used (n=24) 1,377.5 U/kg/week (300-15,000); dosage at which response was obtained (n=14) 721.4 U/kg/week (300-1,500). The response rate was 17/32 patients (53.1%). In a univariate analysis we found no significant differences ($p>0.05$) with respect to any of the parameters considered. However, differences approached statistical significance with respect to sex ($p=0.07$), sEPO ($p=0.07$) and PRBC/m ($p=0.13$). Table 3 shows the differences between responders and non-responders and their statistical significances. One consideration can also be made; if we exclude, from among the responders, the only heavily transfused patient differences with respect to PRBC/m become significant ($p=0.04$). All but one responding patient had a basal sEPO $\leq$ 123 mU/mL, and this was the best cut-off point found (sensitivity 0.86; specificity 0.87). Multivariate analysis could not be performed as the number of patients was low and not all the data were available.

Ten of the twenty patients who were transfusion-dependent become transfusion-independent and six of the seven non-transfusion-dependent patients responded. The duration of response is known in 7 patients (in months): 10+, 16+, 7, 6, 9, 9, 6+ respectively. The only effect on other hematological series concerns platelets which decreased in 2 patients and increased in another two. However, four studies do not provide any information on this point. In 3 patients (n=14) aggravation of splenomegaly was observed and in two of these the size of the spleen decreased after reducing or suspending treatment; in

Table 3. Comparison between responding and non-responding patients. Statistical significance in the univariate analysis.

	Responders	*Non-responders*	*p**
Sex (M/F)	7/7	9/1	0.07
Age (years)	66.2 (SD±8.2)	62.3 (SD±15.3)	0.77
Basal Hb (g/dL)	8.2 (SD±1.6)	8.0 (SD±0.9)	0.77
Basal sEPO (mU/mL)	175.1 (SD±325.4)	922.0 (SD±841.2)	0.07
Transf. Dep (PRBC/mL)	2.1 (SD±3.0)	4.4 (SD±3.4)	0.13
Dosage (U/Kg/week)	721.4 (SD±299.8)	2296.0 (SD±4486.9)	0.26

**Significance limit p<0.05; M/F = male/female; sEPO = serum erythropoietin; Trans. dep (PRBC/m) = transfusional dependency (units of packed red blood cells/month); dosage = maximum dosage used.*

another 4 a reduction of the splenomegaly was observed. Three of these were treated simultaneously with interferon. Five patients (n=29), three of whom responded, received simultaneous HU. Another three received interferon (IFN) simultaneously: all responded. No adverse effects have been reported; one patient died due to myocardial infarction and in another, evolution to acute myeloid leukemia was observed.

Discussion

Anemia is a consistent finding in MMM. Though the origin of this myeloproliferative disorder is unknown, several factors have been considered as possible causes of anemia: ineffective erythropoiesis,[16] inappropriate erythropoietin response to anemia[10] and bone marrow fibrosis.[13] Recently, Barosi *et al.*[19] reported that 87% of patients with MMM presented with elevated levels of sEPO according to their degree of anemia and postulate that anemia is not due to an inappropriate secretion of erythropoietin but to a defective response to it. Some of these causes are shared by other pathologies derived from stem cell disorders such as MDS in which rHuEPO has been widely used with moderate success[20,21] in comparison with other pathologies in which levels of sEPO are considered *low* such as renal dialysis patients,[22] HIV-infected patients in treatment with AZT[23] or anemic cancer patients.[24] The treatment of anemia in MMM has long been mainly transfusional, but the developement of rHuEPO has theoretically provided a new tool. Though Barosi *et al.*[19] believed that no beneficial effect could be expected from this treatment in those patients with high endogenous levels of sEPO and Eschbach *et al.*[22] reported that those patients with end-stage renal disease who presented with myelofibrosis did not respond to rHuEPO, several authors have used it in the treatment of anemia in MMM (Table 1).

Attention must be drawn to several aspects of the statistical analysis: a) it seems that patients with lower transfusional requirements respond better (differences did not reach statistical significance, p=0.13). In fact, six of the seven transfusion-independent patients showed response and the rest of the responders but one received ≤ 3 PRBC/m, while all but three of the non-responders received more than this quantity. If we exclude the only heavily transfused responder patient differences reach statistical significance (p=0.04); b) patients with lower levels of sEPO respond better than those with higher levels (differences are almost significant, p=0.07). From these data a cut-off point of 123 mU/mL of sEPO was the most effective to identify those patients with a higher possibility of being responders; all patients but one with sEPO levels above this were not responders. This cut-off point is lower than that previously reported by our group (250 mU/mL)[25] or by Hellström-Lindberg (200 mU/mL)[20] in patients with myelodysplastic syndromes but is slightly higher than that reported by Rose *et al.*[21] or Cazzola *et al.*[26] (in both cases 100 mU/mL) in patients with the same diagnosis. Differences with respect to sex nearly reached statistical significance (p=0.07) and could be explained by the fact that females had lower levels of sEPO and transfusional needs. However, all these conclusions must be taken with caution as the number of patients in the analysis was small. In overall terms our results suggest that the patients with the best medullary or extramedullary functional reserves, those with lower transfusional requirements and those with lower sEPO levels as well respond better than others. In our experience, patients in the terminal stage of the disease do not benefit from rHuEPO treatment.

It is interesting to point out that though in dogs rHuEPO has been found to produce myelofibrosis this has not been observed in hemodialyzed patients.[27] We have found no data regarding this circumstance except in one patient in whom fibrosis did not progress after 9 months of treatment,[15] but it would be interesting to study more patients to observe whether the degree of fibrosis progresses more rapidly in these patients than in others not treated with rHuEPO.

A question still to be answered is whether the concomitant use of HU could improve the results obtained using rHuEPO alone. This combination has been used successfully to improve anemia in beta-thalassemic patients,[28] and it is known that HU has been used in patients with MMM to reduce splenomegaly, leukocytosis or thrombocytosis and to increase Hb as well as to improve their clinical status with the advantage that the leukemogenic effect is minimal.[29,30] In our experience, those patients treated with HU (patient #1, who did not finish the study, and patient #3) did not respond although another 4 patients in the literature received this treatment and,

of these, three responded, so, in overall terms, 60% of patients treated simultaneously with HU showed response. All the three patients who received simultaneous IFN responded. However, the authors of that report[18] believe that the response could have been due to the fact that all these patients were in the proliferative phase of the disease. In the same report another 4 patients were treated with a combination of GM-CSF, rHuEPO and IFN. All responded. This is the only article reporting a combination of growth factors in the treatment of MMM.

Splenomegaly is another consistent finding in MMM and is a consequence of the extramedullary foci of hemopoiesis. In our patients aggravation of splenomegaly while being treated with rHuEPO was observed in patient #1 but we believe this to be due mainly to progression of his disease. However, 2 cases have been reported,[9,10] in which this increase of the splenic size was observed and in both the size of the spleen reduced after discontinuing treatment. The concomitant use of HU or IFN could perhaps avoid this enlargement of the spleen. In one of our responding patients, splenomegaly disappeared with rHuEPO treatment. This effect has been previously reported in four patients.

Effects of rHuEPO on the other hematological series seem to occur rarely and have affected only platelets. In one of our patients the platelet count almost doubled. In the literature, another patient experienced an increase, while two suffered a decrease in their platelet counts. The evolution of MMM to acute myeloid leukemia is well known, but the only episode registered in these patients was observed, not while receiving treatment, but 7 months later.

In conclusion, rHuEPO can be an effective treatment for anemia in patients with MMM, especially in those with low sEPO (≤ 123 mU/mL) levels and low transfusional dependency (≤ 3 PRBC/m). Female sex was also associated with a better response. However this could be due to a more stable situation in their disease (with both lower sEPO levels and lower transfusional dependency). However, due to the high cost of treatment we believe that this should be considered in the light of the life expectancy of patients and their quality of life. In addition, our conclusions are based on the results obtained in a few patients and further studies with a greater number of patients are required for confirmation.

Contributions and Acknowledgments

DP and JNR were responsible for the design of the study. MLM, JNR and JCD contributed to the execution of the study. All the authors contributed to the analysis and writing of the paper. Though all authors have contributed substantially in the article, the authors are ordered according to their contribution in the final form of the article.

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Disclosures

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Manuscript processing

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References

1. Mittelman M, Lessin LS. Clinical application of recombinant erythropoietin in myelodysplasia. Hematol Oncol Clin North Am 1994; 8:993-1009.
2. Bourantas KL, Tsiara S, Makis A, et al. Recombinant human erythropoietin for the treatment of anemia in chronic myelogenous leukemia. Eur J Haematol 1997; 59:263-5.
3. Balleari E, Gatti AM, Mareni C, Massa G, Marmont AM, Ghio R. Recombinant human erythropoietin for long-term treatment of anemia in paroxysmal nocturnal hemoglobinuria. Haematologica 1996; 81:143-7.
4. Besa EC, Nowell PC, Geller NI, Gardner F. Analysis of androgen response of 23 patients with agnogenic myeloid metaplasia. Cancer 1982; 49:308-13.
5. Manoharan A. Management of myelofibrosis with intermittent hydroxyurea. Br J Haematol 1991; 77:252-4.
6. Rodríguez JN, Martino ML, Muñiz R, Prados D. Recombinant human erythropoietin for the treatment of anemia in myelofibrosis with myeloid metaplasia. Am J Hematol 1995; 48:135-6.
7. Laszlo J. Myeloproliferative disorders (MPD): myelofibrosis, myelosclerosis, extramedullary hematopoiesis, undifferentiated MPD, and hemorrhagic thrombocythemia. Semin Hematol 1975; 12:409-32.
8. Frutchman SM, Scigliano E, Wasserman LR. Recombinant erythropoietin (rHuEPO) can be an effective agent in transfusion dependent myelofibrosis. Blood 1990; 76:271a.
9. Iki S, Yagisawa M, Ohbayashi Y, Sato H, Urabe A. Adverse effect of erythropoietin in myeloproliferative disorders. Lancet 1991; 337:187-8.
10. Cazzola M, Ponchio L, Beguin Y, et al. Subcutaneous erythropoietin for treatment of refractory anemia in hematologic disorders. Results of a phase I/II clinical trial. Blood 1992; 79:29-37.
11. Mittelman M, Floru S, Djaldetti M. Subcutaneous erythropoietin for treatment of refractory anemia in hematologic disorders. Blood 1992; 80:841.
12. Rafanelli D, Grossi A, Longo G, Vannucchi AM, Bacci P, Ferrini PR. Recombinant human erythropoietin for the treatment of myelodysplastic syndromes. Leukemia 1992; 6:323-7.
13. Aloe Spiriti MA, Latagliata R, Avvisati G, et al. Erythropoietin treatment of idiopathic myelofibrosis. Haematologica 1993; 78:371-3.
14. Mohr B, Herrmann R, Hunh D. Recombinant human erythropoietin in patients with myelodysplastic syndrome and myelofibrosis. Acta Haematol 1993; 90:65-70.
15. Ziegler ZR, Rosenfeld CS, Shadduck RK. Resolution of transfusion dependence by recombinant human erythropoietin (rHuEPO) in acquired pure red cell aplasia (PRCA) associated with myeloid metaplasia. Br J Haematol 1993; 83:28-9.
16. Tefferi A, Silverstein MN. Recombinant human erythropoietin therapy in myelofibrosis with myeloid

metaplasia. Br J Haematol 1994; 86:893.
17. Falkson CI, Keren-Rosenberg S, Uys A, Falkson G, Stevens, Vermaak WJ. Recombinant human erythropoietin in the treatment of cancer-related anaemia. Oncology 1994; 51:497-501.
18. Bourantas KL, Tsiara S, Christou L, et al. Combination therapy with recombinant human erythropoietin, interferon-α-2b and granulocyte-macrophage colony-stimulating factor in idiopathic myelofibrosis. Acta Haematol 1996; 96:79-82.
19. Barosi G, Liberato LN, Guarnone R. Serum erythropoietin in patients with myelofibrosis with myeloid metaplasia. Br J Haematol 1993; 83:365-9.
20. Helström-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.
21. Rose EH, Abels RI, Nelson RA, McCullough DM, Lessin L. The use of rHuEPO in the treatment of anemia related to myelodysplasia (MDS). Br J Haematol 1995; 89:831-7.
22. Eschbach JW, Abdulhadi MH, Browne JK, et al. Recombinant human erythropoietin in anemic patients with end-stage renal disease. Results of a phase III multicenter clinical trial. Ann Intern Med 1989; 111:992-1000.
23. Henry DH, Beall GN, Benson CA, et al. Recombinant human erythropoietin in the treatment of anemia associated with human immunodeficiency virus (HIV) infection and zidovudine therapy. Overview of four clinical trials. Ann Intern Med 1992; 117:739-48.
24. Henry DH. Clinical application of recombinant erythropoietin in anemic cancer patients. Hematol Oncol Clin N 1994; 8:961-73.
25. Rodríguez JN, Diéguez JC, Prados D. Erythropoietin in the myelodysplastic syndromes: meta-analytical study. Br J Hematol 1995; 91:254.
26. Cazzola M, Ponchio L, Pedrotti C, et al. Prediction of response to recombinant human erythropoietin (rHuEPO) in anemia of malignancy. Haematologica 1996; 81:434-41.
27. Tulliez M, Picard F, Casadevall N, et al. Human erythropoietin does not induce bone marrow fibrosis in hemodialysed patients. Nephrol Dial Transpl 1989; 4:674-5.
28. Aker M, Perry D, Dover G, Rachmilewitz EA. The effect of combined recombinant human erythropoietin and hydroxyurea on erythropoiesis in β-thalassemia intermedia. Blood 1994; 84:257a.
29. Kaplan ME, Mack K, Goldberg JD, Donovan PB, Berk PD, Wasserman LR. Long-term management of polycythemia vera with hydroxyurea: a progress report. Semin Hematol 1986; 23:167-71.
30. Nand S, Stock W, Godwin J, Fisher SG. Leukemogenic risk of hydroxyurea therapy in polycythemia vera, essential thrombocythemia, and myeloid metaplasia with myelofibrosis. Am J Hematol 1996; 52:42-6.