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High-doses epoetin alpha in patients with multiple myeloma-related anaemia: early response and effective maintenance treatment with a longer dosing interval

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Abstract. In this report we analyse the results of a pilot and open study on the management of the disease-related anaemia in patients with multiple myeloma, evaluating the efficacy and tolerability of a new regimen using high doses of erythropoietin-alpha (Epo-alpha, 40,000 IU) given twice weekly. Patients who responded to initial treatment continued on maintenance treatment with Epo-alpha given at a longer dosing interval. Intravenous iron supplementation was given during the first four weeks of treatment and periodically, if required, during the maintenance phase. Transfusions were given according to clinical criteria. Overall, 9 out of 10 patients (90%) responded to treatment. Out of these, 8 achieved the correction of anaemia within the first four weeks of treatment, with a median response time of 2 weeks (range: 1-4 weeks), and one patient showed a late response, becoming transfusion independent after 7 weeks. This new dosing regimen achieved a rapid erythroid response in high percentage of patients and permitted to titrate treatment as necessary to maintain stable haemoglobin values.

Key words: anemia • multiple myeloma • erythropoietin • epoetin alpha

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INTRODUCTION

Anaemia is one of the most common clinical findings in patients with multiple myeloma (MM). A number of mechanisms may contribute to its development: myelosuppressive effect of chemotherapy, anaemia of chronic disease, including a decreased erythrocyte survival, a relative erythropoietin (Epo) deficiency and a diminished marrow response to erythropoietin due to the presence of inflammatory cytokines[1]. Additionally, such cytokines (tumor necrosis factor-alpha and interleukines 1 and 6) may contribute to the diminished Epo production by the kidney[2], the decreased responsiveness of erythroid progenitors to Epo[3,4] and the impairment of iron metabolism[5]. Recently, erythroblasts cytotoxicity, promoted by highly malignant myeloma cells which over-express Fas-ligand and TRAIL receptors, has been considered as another critical event in the pathogenesis of anaemia in MM patient with advanced and progressive disease[6]. Several trials have demonstrated that recombinant human Epo (epoetin) can significantly reduce transfusion requirements and improve the patient's quality of life[7-10].

The current recommended initial dose of epoetin

in MM anaemic patients is 150 U/Kg subcutaneously (SC)3 times a week[11]. This dose can be doubled if an adequate response does not occur after 4 weeks of therapy[12]. In patients with B-chronic lymphoproliferative disorders-related anaemia responding to epoetin treatment, the need of long-term maintenance treatment to sustain the response has been demonstrated[13]. Recent data from a trial involving a large number of patients with cancer-associated anaemia, has established that the administration of 40,000 IU of epoetin, SC, once weekly was well tolerated and was as effective as the standard three times weekly regimen[14].

So far, the potential role of high-dose (HD) epoetin in the treatment of the MM associated- anaemia has not been extensively investigated. We carried out a pilot study to evaluate the efficacy and tolerability of a new dosing regimen with HD epoetin-alpha (epoetin-α) for the management of MM-related anaemia.

PATIENTS AND METHODS

The aim of this study was to evaluate the efficacy of HD epoetin-α administered twice weekly in correcting anaemia in patients with MM, as well as to evaluate the effectiveness of a maintenance treatment with epoetin-α given at a longer dosing interval. Patients with MM-related anaemia, presenting an haemoglobin (Hb) concentration less than 10g/dl, were enrolled in this non comparative pilot study. Patients with anaemia that could be related to other diagnosed causes of anaemia were excluded. Table 1 shows the patient's clinical features. Diagnosis of MM was established according to the Durie and Salmon staging system [15]. A total of 10 patients entered in the study: 5 males and 5 females with a median age of 72 (45-87) years. Nine patients were in IIIA and one in IIA disease stage. Median time from diagnosis to initiation of epoetin-α was 38 months (range: 1-74 months). The median number of the previous lines of anti-myeloma treatments was 2 (range: 0-5). Five patients, of whom 2 were transfusion-dependent, had relapsing or refractory disease and received a concomitant treatment with thalidomide plus dexamethasone (Table 1). One of these, presenting a 90% malignant plasma cells associated with some abnormalities of residual erythroid precursors, such as multinuclearity, karyorrhexis, internuclear bridges, cytoplasmic vacuolation and increased iron in the macrophages but no evidence of blasts on the bone marrow (BM) smears, entered also into the trial after the detection of no karyotypic abnormality by conventional cytogenetic analysis. Although a secondary myelodysplastic syndrome, probably related to the heavy previous alkylating therapies, was suspected on morphological basis we believed that in the development of the severe anaemia the major role was due to the MM progression and that the others abnormality detected on the BM were responsible for only a minimal contribution. Two patients were at the onset of disease: the first was on melphalan plus prednisone and the second on a multi-chemotherapy regimen prior to a planned allogeneic bone marrow transplantation (BMT). Three patients were in plateau phase and were treated with a single monthly infusion of pamidronate (90 mg) or zolendronate (4 mg) associated with dexamethasone (40 mg). The mean (±SD) baseline Hb value was 8.5±0.7 g/dl. The median performance status score was 1 (0-3). The mean (±SD) serum erythropoietin level, measured in six

Table 1. Patient's characteristics

Patient	Age (years)	Stage[15]	M-protein (isotype)	M-protein serum level (gr/dl)	β-2 microglobulin (mg/dl)	Hb (gr/dl)	Serum Epo (mU/l)	Serum Ferritin (ng/dl)	Serum Iron (mcg/dl)
1	87	III A	Ig A-κ	3.2	7.3	8.2	27	353	58
2	72	III A	Ig A-λ	2.7	4.1	7.5	49	225	66
3	86	III A	Ig G-κ	3.3	Not done	8.0	Not done	144	23
4	63	IIIA	Ig G-κ	5.7	7.8	8.0	56	327	61
5	45	III A	Ig G-λ	4.6	2.0	7.8	68	101	105
6	50	III A	Ig G-λ	2.2	3.4	8.8	Not done	109	244
7	72	II A	Ig G-κ	2.7	2.4	9.2	41	28	64
8	77	III A	Ig G-λ	1.6	3.5	9.0	20	98	70
9	64	III A	Ig G-λ	4.2	6.4	9.4	Not done	476	137
10	75	III A	Ig G-κ	3.7	2.8	9.2	Not done	159	59

patients, was 43±17 mU/ml. All patients received IV iron supplementation during epoetin-α therapy, although serum ferritin values were normal or elevated. All patients were properly informed and gave their consent.

Study design: epoetin-α 40,000 U, was given twice weekly (TW), SC, for 4 weeks or shorter period if Hb level was ≥12 gr/dl. Unresponsive patients continued to receive the same treatment for up to 8 weeks. In patients presenting an Hb value higher than 14.0 gr/dl epoetin-α has to be withdrawn. After the induction phase, based on the maintained response to epoetin-α, evaluated every two weeks, the dosing interval was progressively longed. The responders received epoetin-α 40,000 U once weekly (OW) for two weeks and then, if maintaining an Hb level above 12.0 gr/dl, the same dose was given every two weeks while the other responders with an Hb concentration lower than 12.0 gr/dl continued to receive a weekly dose. In patients presenting an Hb value higher than 13.0 gr/dl the dosing interval was prolonged to three weeks. The previous dosing interval was restarted in patients presenting a drop in the Hb value more than 1 gr/dl. Intravenous (IV) iron supplementation (gluconate iron, 125 mg/week) was given by very slow infusion during the first four weeks of treatment, with the aim of avoiding the functional iron deficiency and optimising the response to epoetin-α. The same iron IV supplementation was administered to responding patients in maintenance therapy only if hypochromic erythrocytes were >10% of the total or transferrin saturation <20%. Transfusions were given according to clinical criteria, usually when the haemoglobin concentration was less than 8 gr/dl or in case of organ-related symptoms referred to anaemia. Major response was defined as an increase of the Hb level by ≥2 gr/dl and complete absence of blood transfusion requirements; minor response was defined as an increase of the Hb level by ≥1 gr/dl and complete absence of blood transfusion requirements.

RESULTS

The response to HD of epoetin-α and the patient's clinical course are summarized in table 2. Overall, 9 (90%) of 10 patients responded to the treatment: 2 achieved a minor response and 7 a major response. Out of these, 2, 3, 2 and 1 achieved the response within the first, the 2nd, the 3rd and the 4th week respectively, reaching a mean (±SD) Hb level of 12.6±1.5 gr/dl, and one showed a late response, becoming transfusion independent after 7 weeks. The median response time was of 2 weeks (1-7). The patient with the associated erythrodysplasia was unresponsive to epoetin-α and the treatment was withdrawn at the 8th week. Out of the 9 responders, 3 stopped the treatment after 10, 18, 26 weeks respectively; the first died because of an unrelated MM illness, the second is well after an allogeneic BMT and, to date, presents normal Hb values and no need for anti-anaemic treatment; the third died because of a massive skeletal and pulmonary MM involvement. One patient, who had a very aggressive MM progression after a partial remission of MM disease achieved by the combination of thalidomide plus dexametasone, lacked the response requiring red blood cells (RBC) transfusions after 52 weeks of treatment with epoetin-α.

To date, five patients have a sustained response at a median time of 24 weeks (range: 18-42 weeks). Out of these, two patients presented progressive and advanced disease phase; the first is receiving OW dosage of epoetin-α, the second is on TW dose regimen, because a drop in Hb value to <9 gr/dl was observed after 2 months of successful treatment with the weekly dosage. This patient recovered to the previous Hb level after restarting the TW schedule, avoiding transfusion. Patients, who were in plateau phase of the disease, are being treated with 40.000 U epoetin-α administered every two weeks from the 26th, 20th and 10th week respectively. Longer time interval (three weeks) between administration period was ineffective to maintain a steady Hb value in these three patients. No patients presented an Hb values higher than 14.0 gr/dl. The HD epoetin-α and the IV iron supplementation were well tolerated and no adverse events occurred.

DISCUSSION

In the past, RBC transfusion was the only treatment option for the management of anaemia in patients suffering from MM, inducing a rapid rise in Hb level. However, the gain in Hb level is modest and transient, and Hb values return to baseline within a short period of time. In addition, transfusions are associated with a high risk of complications that may limit their effectiveness and also have a significant impact on health care cost. According to the current published data, the costs of transfusions are often overlooked and underestimated, even if this approach is generally con-

Table 2. Disease phase at the starting of epoetin-α and outcome.

Patient	Time from onset (months)	Previous treatments	Disease phase	Concomitant Treatment	Disease Outcome	Response to Epoetin-α
1	40	MP	Relapse	Thal+ Dex, Biphosphonates	Stable disease	Minor
2	41	MP	Relapse*	Thal+Dex, Biphosphonates	Progression	No
3	33	MP	Plateau	Biphosphonates +Dex	Stable disease	Major
4	74	VAD, APBSCT, IFN, CTX, MP	Progression	Thal + Dex, Biphosphonates	Stable disease	Minor (late response)
5	2	None	Onset	VAD, Biphosphonates	Partial remission	Major
6	17	VAD, APBSCT, IFN	Plateau	Biphosphonates + Dex	Stable disease	Major
7	1	None	Onset	MP, Biphosphonates	Partial remission	Major
8	35	MP	Plateau	Biphosphonates + Dex	Progress	Major
9	56	VAD, APBSCT, IFN	Relapse	Thal+Dex, Biphosphonates	Partial remission	Major
10	16	MP	Relapse	Thal+Dex, Biphosphonates	Progression	Major

*Erytrodysplasia; VAD: vincristine, adriamycin and dexamethasone (Dex); MP: melphalan plus prednisone; APBSCT: autologous peripheral blood stem cells transplantation; IFN: interferon; CTX: cyclophosphamide; Thal + Dex: thalidomide 100-200 mg/day plus Dex 40 mg/day, D1-D4 every 4 weeks; Biphosphonates + Dex: single montly infusion of pamidronate (90 mg) or zolendronate (4 mg) plus Dex 40 mg; SD: stable disease; Prog.:progression; PR:partial remission.

sidered less expensive than other alternatives[16,17]. In contrast, epoetin is a well-known effective treatment in managing the anaemia related to MM and its durable effects and sustained benefits have been shown in a number of studies. In general, about two thirds of patients achieve a significant haematological response with the standard recommended dosage of 10.000 U three times a week[18]. Alternatively, epoetin-α may be administered at a dose of 40.000 U once a week[14]. A dose-response effect has been clearly demonstrated[19], although the correction of anaemia in some patients could require higher doses than those reported as effective, while the optimal dose and the dosing regimen are not predictable in all patients[20,21]. Although epoetin-α efficacy in the enhancement of erythropoiesis in the large part of MM patients has been demonstrated, there is a number of patients that do not respond to treatment[22]. Functional iron deficiency has been reported as the most important cause of low response to epoetin-α [23,24]. We included IV iron supplementation during TW epoetin-α administration, in order to support the increased erythropoiesis. In the maintenance phase iron supplementation was given when functional iron deficiency was present[10,11].

The importance of a rapid and effective correction of severe anaemia (Hb ≤8 g/dl) should not be underestimated in order to reduce the risk of transfusion and to improve the symptoms of anaemia and the patient's quality of life[25]. This is particularly crucial for the elderly patients who are considered more vulnerable. In these subjects, the haematological response to epoetin-α standard dosing regimen may be considered clinically inadequate in order to aim a rapid and sustained response. In our pilot trial we tested a new treatment schedule with HD epoetin-α to ameliorate severe anaemia related to MM. The treatment resulted in a rapid correction of anaemia in 8 out of 10 patients, with a final overall response of 90%. The mean Hb level rose from 8 g/dl to 12.6 g/dl after 4 week of treatment. Another interesting finding is the possibility to maintain a long-term haematological response with 40.000 U epoetin-α every two weeks, as we followed-up three patients. It is not absolutely clear how HD epoetin-α acts over increasingly long intervals

between administrations. It is well known that the standard doses of epoetin-α, which retains the same natural amino acid sequence and glycosylation seen with natural hormone, administered three times a week stimulate the proliferation and prevent the apoptosis of the colony-forming-unit-erythroid (CFU-Es). In a recently published study on the effects of standard doses of epoetin-α, combined with intermittent courses of all-trans retinoic acid in patients with myelodysplastic syndromes, the increase of Hb concentration in responders was found in association with higher concentrations of BFU-Es in the peripheral blood[26]. Some rather biological properties of epoetin-α, such as the reported effects on the Central Nervous System[27] and the antitumour activity, are still unclear and are currently under investigation. In a recent study, a tendency for prolongation of life in cancer patients treated with epoetin-a has been reported[28]. Studies in mice MM model have shown tumour regression in response to the addiction of epoetin-α[29].

Whether these aspects may really contribute to improve the management of anaemia in patients with MM and other lymphoproliferative disorders remain to be determined and deserve further clinical and biological researchers, such as bone marrow culture investigations and others in vitro study. Our study, including a very heterogeneous cohort of patients, most of all presenting very advanced and refractory disease and all receiving concomitant anti-myeloma treatments, had not been designed to detect neither these suggested effects of epoetin-α by biological studies nor the difference in survival, given the lack of a control population. Nevertheless, all the three patients in plateau phase of disease, receiving the same maintenance anti-myeloma treatment with a single monthly infusion of zolendronate plus dexamethasone, showed a slowly but progressively increasing of the serum paraprotein levels, even if in no of these the clinical features of the relapse were observed.

Despite the clear limitations of our experience, which don't permit to draw any definitive conclusion, given the limited number of patients and the inadequate study design, the preliminary data are promising. Our observations suggest that this high dose regimen is safe and effective in quickly correcting severe anaemia, although the potential anti-anaemic effects of the anti-myeloma treatments may have affected the haematological response. Further, the value of these results is limited by the fact that in a population of 10 patients the 95%-confidence limit of the observed response rate (90%) extends down to below 40%. We suggest that this pilot study could be used as the basis for the schedule of other larger trials, although did not allow us to fully support the superiority of the HD epoetin-α over the standard dose. In conclusion, this new dosing regimen determined a rapid erythroid response in high percentage of patients, permitting to titrate treatment as necessary to maintain stable Hb values and suggesting that the use of HD epoetin-α could have an extended role in the management of anaemia in MM patients.

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