The Effect of Subcutaneous Recombinant Human Erythropoietin (r- HuEPO) on Anemia in Cancer Patients Receiving Platinum-Based Chemotherapy

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Abstract

Advanced cancer is commonly associated with significant anemia which worsens with the administration of cytotoxic drugs. Erythropoietin (EPO) levels in these patients are usually inappropriately low for the degree of anemia. We evaluated the effect of subcutaneous administration of recombinant human erythropoietin (r-HuEPO) on hematologic parameters and transfusion requirements in anemic cancer patients who were receiving platinum-based chemotherapy. Baseline studies included complete hemogram, reticulocyte count, serum iron, TIBC, ferritin and determination of performance status and quality of life (QOL). Twenty-three patients, 13 females, 10 males with mean age 52 years received 150 units/kg of r-HuEPO three times weekly for a minimum of 10 weeks. They also received supplemental iron. Ovarian cancer was the commonest underlying malignancy. Most of the patients received platinum-based combination chemotherapy. Mean duration of r-HuEPO therapy was 12.6 weeks. Average baseline reticulocyte count was 1.8% which increased to 7.0% after one week therapy. Eight patients had normalization of hemoglobin values. Another eight patients improved their hemoglobin by at least 2 g/dl, however, hemoglobin values remained below the normal range. Two patients had only slight increase in hemoglobin but never required blood transfusion. Three patients who were transfusion dependent had decrease in the transfusion requirements. Two patients had no significant benefit. In most patients response was evident within 2 weeks. All responders had improvement in QOL. No significant toxicity was observed. We conclude that r-HuEPO, given subcutaneously, is highly effective in amelioration of anemia and prevention of or reduction in transfusion requirements in cancer patients receiving platinum-based chemotherapy (JPMA 48:127,1998).

Introduction

Anemia is commonly observed complication in the cancer patients. It has been reported in upto 30% of patients with solid tumors. It is particularly common in those at an advanced stage of their disease[1-3]. Although several mechanisms may account for the anemia observed in these patients, it is frequently without any obvious etiology and is often categonzed as anemia of chronic disease. This condition is characterized by erythroid hypoplasia of the bone marrow, decreased red cell production, normocytic or microcytic red cell indices and a slightly decreased red cell survival. Serum iron is generally low as is the total iron binding capacity (TIBC) but the serum iron to TIBC ratio is usually within normal range. Despite adequate bone marrow iron stores. there is an inability to utilize iron for hemoglobin synthesis resulting in a reticulo-endothelial block.

The anemia observed in cancer patients has an adverse effect on their quality of life. These patients are often symptomatic due to anemia with resultant weakness, fatigue, drowsiness, lethargy, depression and in extreme circumstances, respiratory distress and cardiac decompensation. Allogeneic blood products are frequently required for amelioration of anemia and alleviation of symptoms. Multiple blood transfusions, however, can be hazardous. They can result in spread of infections suchasviral hepatitis,

AIDS, cytomegalovirus and Epstein Barr virus and occasionally toxoplasmosis and malaria. Transfusion also carry the risk of severe allergic reactions and the problems consequent of iron overload[4-6]. It has also been suggested that allogeneic blood transfusion can induce immunosuppression which can adversely effect the survival of already ininiunocompromised patients[7-13]7-13.

In cancer patients, anemia can also be caused or aggravated by cytotoxic therapy. This anemia may be induced by direct myelotoxic effect of the chemotherapeutic agents or indirectly by drug-induced renal damage resulting in low levels of EP0[14-16]. Cisplatin is one of the most widely used cytotoxic agents. Approximately 40% of cancer patients treated with cisplatin develop normocytic norrnochromic anemia with a low reticulocyte count. Many patients with initial normal blood counts, subsequent to chemotherapy, develop anemia. Most of them require blood transfusions. Although exact mechanism of cisplatin-induced anemia is not known, it appears that inadequate EPO response plays an important role in its pathogenesis[17-19]. The ordinarily linear relationship between hemoglobin concentration and circulating EPO levels is not observed in these patients and despite anemia, plasma EPO levels are inappropriately low. This inadequate response is thought to be due to cisplatin associated nephrotoxicity. Although renal function appears to be intact in most of the patients during cisplatin therapy, sub-clinical nephrotoxicity resulting in damage to the renal oxygen sensor and EPO release cannot be entirely excluded. Hence, relative deficiency of EPO appears to play an important role in anemia caused by cytotoxic therapy, particularly with platinum compounds.

Availability of r-HuEPO has resulted in its use in several situations where anemia is caused by absolute or relative deficiency of EPO[20]. R-HuEPO has been demonstrated to alleviate anemia in patients with end-stage renal disease and HIV infected patients receiving zidovudine[21-23]. In animal studies, cisplatin associated anemia responds to exogenous EPO24. Because of success and those receiving cisplatin may be similar to anemia of chronic disease, use of r-HuEPO may be worthwhile.

We studied the effect of r-HuEPO given subcutaneously to cancer patients who developed anemia while receiving platinum-based chemotherapy. We report our experience with the initial 25 patients.

Patients and Methods

This study is an open-label, non-comparative evaluation of the efficacy and safety of r-HuEPO in cancer patients with anemia. Only patients with non-hematologic tumors receiving either cisplatin or caiboplatin based chemotherapy were included in this trial. Patients were closely followed during the study. Physical examination was repeated on weekly bases and blood tests were done as necessary. R-HuEPO (EPREX) was provided by Cilag Limited (a subsidiary of Johnson and Johnson) as a sterile, buffered solution containing 2.5 mg/mI human serum albumin. It was supplied in vials containing 10,000 units/mI. All vials were stored refrigerated between
2-8°C. It was injected subcutaneously three times a week, on ambulatoiy basis, by the patients or their relatives, mostly into the thigh.

Patients selection: Patients entered on the study were required to have histologically proven diagnosis of cancer. They should have been receiving cisplatin or carboplatin-based chemotherapy which needed to be continued for at least another 10 weeks. Patients were also expected to be _18 years of age, hemoglobin level of< 10.5 g/dl, a life expectancy of _4 months, Eastern Cooperation Oncology Group (ECOG) performance status (PS) of 0-3, nonnal neutrophil and platelet counts, creatinine <2.0 mg/dl and creatinine clearance >50 ml/min.. Patients were also required to have no other obvious cause of anemia such as blood loss, nutritional deficiency or hernolysis.

Exclusion criteria: Patients with cerebral metastases, uncontrolled hypertension, recent acute illness. history of seizures, recent surgery or radiation therapy, hematologic malignancy, androgen therapy

within the last two months, or those receiving any other experimental drug were excluded. Similarly, patients with clinically significant dysfunction of pulmonary, cardiovascular, endocrine, neurological, gastrointestinal or genito-urinary systems not attributable to underlying malignancy were also excluded from the trial.

Baseline studies: Prior to the institution of r-HuEPO therapy, the procedures carried out on all patients included complete history and physical exanunation, several laboratory tests including complete hemogram, reticulocyte count, serum iron levels and total iron binding capacity, hepatic and renal function tests, stool for occult blood, direct coombs test and determinatin of performance status (PS) and quality of life (QOL).

Study design: All eligible patients were instructed to self administer r-HuEPO at a dose of 150 unit/kg three times a week subcutaneously, mostly into the thigh, fora minimum of 10 weeks. Patients also received ferrous sulfate 200 mg three times a day.

Evaluation of response: The major efficacy criteria were the effects of treatment on hematocrit and transfusion requirements. This was done by comparing the baseline and final values of reticulocyte count, hemoglobin and hematocrit. Complete response was defined as no transfusion requirement and achievement of hemoglobin more than 12 gm/dl. Those patients who had an increase in hemoglobin of _2 gms/dl, became transfusion independent, but did not achieve hemoglobin of _12 gm/dl, were considered as partial responders. Patients who had stabilization of their hemoglobin, required no furtherblood transfusions, but failed to achieve a hemoglobin increase of >2 gm/dl were considered to have stable disease. All others who required blood transfusions were considered as failures.

In this study, we also assessed the impact of r-HuEPO therapy on QOL parameters. Both before and after the study, patients responded to a questionnaire composed of visual analogue scales (VAS) designed to assess their energy level, ability to perform daily activities and overall QOL . Each question was answered by placing a vertical mark on a 10 cm line representing a continum from the lowest to the highest assessment for that item.

Results

Demographic features and baseline clinical characteristics

Total number of patients enrolled in the study were 25. Two patients were excluded because they received non-platinum based therapy. Meanage of the patients was 52.0 years. The commonest underlying malignancy was ovarian cancer. Eleven patients received cisplatin 100 mg/m^2 while fourteen were treated with caiboplatin 400 mg/m^2 administered every 3-4 weeks. Average number of cycles given after initiationof r-HuEPO was three. Most patients had ECOG PS of 3. The clinical characteristics are provided in Table I.

Table I. Demographic and baseline characteristics (n=23).

Age in years (mean±SD)	52.0±14.09
Sex	
Males	10
Females	13
Tumor type	
Ovarian cancer	8
Lung cancer	6
Miscellaneous	9
Chemotherapy regimen	
Single agent carboplatin	3
Platinum-based combination	20
ECOG performance status	
0	1
1	6
2	6
3	10
Transfusion dependent	12
Hemoglobin value (mean±SD)	9.27±1.13
Reticulocyte count (mean±SD	1.82±2.1

Baseline hematologic values included a pre- therapy hemoglobin level of 9.27 mg/dl, reticulocyte count of 1.8%, mean serum iron values of 32 ng/dl and total iron binding capacity of 158. Twelve patients were transfusion-dependent before being enrolled in the study.

Response to therapy

Mean duration of r-HuEPO therapy was 12.6 weeks. Mean hemoglobin level increased from baseline 9.27 g/dl to 11.46 g/dl at the end of therapy (p=0.58). Average reticulocyte count increased from base-line 1.82% to 7.0% after one week of r-HuEPO (p=0.44). Eight patients underwent complete remissionwith correction of anemia to _12 g/dl. An additional eight patients had a partial response to therapy with an improvement in hemoglobin of at least 2 g/dl. Two patients had stabilization of their anaemia and did not require any blood transfusion. Those patients who were previously transfusion dependent had decrease in their transfusion requirements. Two patients respondedpoorly andcontinuedto be anemic and transfusion dependent. Differences observed in transfusion requirement before and after treatment with eiythropoietin are statistically significant (p=0.14). All patients except two non-responders had improvement in their QOL scores. No significant toxicity other than skin reactions was observed. More specifically, none of the patients developed hypertension (Table II).br>

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Discussion

Since the availability of r-HuEPO, several trials have evaluated the efficacy and toxicity of EPO in the correctionof anemia caused by absolute or relative deficiency of EPO20. It has demonstrated efficacy in alleviating anemia in patients with end- stage renal disease and those infected with HIV requiring zidovudine therapy[21-23]. It induces a brisk hematological response provided adequate iron stores are available. In cancer patients, r-HuEPO has been demonstrated to reduce anemia and decrease transfusion requirements in patients with hematologic neoplasms such as multiple myeloma and solid tumors[25-27]. It is also effective in those who develop anemia as a consequence of cytotoxic therapy[28,35]. In the largest study published so far, overall response rate was 48% in those receiving cisplatinversus 58% in patients on non-platinum containing regimen[36]. There was also a significant reduction in transfusion requirements. Response to therapy did not depend upon the underlying tumor

type. Several other studies have also demonstrated that r-HuEPO causes improvement in hemoglobin levels and ameliorates anemia induced by cytotoxic drugs, radiation radiotherapy, or cancer[28-35]. It has also been shown that responses are observed most consistently at doses that are slightly higher than those utilized in patients with renal failure. Most patients require 100 lU/kg/day intravenously to achieve the best response. Some of the studies have also demonstrated improvement in median survival time for those responding to r-HuEPO suggesting that it enables responding patients to lead a more socially and physically active life with increased sense of well being and better QOL[37]. It has also been suggested that response to r-HuEPO improves with the duration of therapy. Results obtained in our study are consistent with these observations.

The route of administration of r-HuEPO may be of significance in determining response to therapy. Subcutaneous administration has been demonstrating as safe and effective therapy of anemia associated with chronic renal failure, myeloma and other hematologic malignancies[38,39]. It also offersthe convenience of administrationonan out-patient basis. Furthermore, slow release from the subcutaneous depots provides lower but more sustained plasma levels than intravenous injections. A recent study that subcutaneous administration of r-HuEPO results in a significant (30%) dose reduction. Studies to determine the best site for subcutaneous injection reveal that injection into the thigh results in more rapid absorption. higher peak concentration and greater
bioavailability than injection in the arm or abdomea We utilized subcutaneous route of administration with r-HuEPO injected into the thigh in all patients. This may be partly responsible for the excellent results obtained in our study.

Several studies have suggested that rate limiting factor in response to r-HuEPO therapy in state of the body iron stores[25-35]. Improvement observed in the hemoglobin levels can be further enhanced by concomitant use of iron. In our study, supplemental iron was provided to all patients.

Due to high cost of r-HuEPO, many investigators have analyzed different factors that may be predictive of subsequent response[30-36]. An increase in reticulocyte count to above 40,000/cmm over the baseline value after 4 weeks of therapy appears to be associated with a higher percentage of responding patients. It has also been suggested that serum transferrin in receptor levels may be the most reliable and earliest predictor of response to r-HuEPO. Baseline serum EPO levels, however, fail to predict response to therapy. Due to small number of patients in our study, we did not systematically study the value of predictive factors. It, however, appears that all patients who responded had a brisk reticulocyte response seen as early as 10 days after initiation of r-HuEPO therapy:

Due to high degree of evolutionaiy molecular conservation, very few patients develop significant immunologic reaction to r-HuEPO. Only one possible instance of neutralizing antibody formation has been descnbed[40]. Side-effects directly attributable to r-HuEPO are few and generally limited to a transient flu like syndrome or burning at the site of injection. In our study, other than an occasional complaint of burning at the injection site, no significant side-effects related to r-HuEPO were observed.

Cost of r-HuEPO therapy is a major problem to its widespread use, particularly in the developing countries. We utilized higher doses in our study. Other investigators have reported clinically significant responses at much lower doses of erythropoietin. Cascinu et al, utilized 50 to 75 units of r-HuEPO/kg three times a week and obtained an impressive clinical response rate[35]. In particular, if subcutaneous route of administration is utilized, it may be possible to achieve equally good results with lower doses of r-HuEPO. This would substantially reduce the cost of therapy.

Another potential use of r-HuEPO is its ability to prevent anemia caused by cytotoxic therapy incancerpatients. Prophylaxis against anemia may be successful at lower doses of eiythropoietin[41]. It may also prevent anemia-related reduction in quality of life of cancer patients receiving cytotoxic therapy and all together eliminate the need for blood transfusions. Such a trial is in progress at our institution.

In conclusion, our study clearly demonstrates the ability of r- HuEPO given subcutaneously at 150 units/kg three times weekly to ameliorate anemia caused by platinum-based chemotherapy in cancer patients. It prevents or reduces the need for transfusion therapy. R-HuEPO therapy is devoid of any serious side-effects and significantly improves the quality of life incancerpatients with anemia.

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