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SCIENCE DIRECT
Gynecologic Oncology 101 (2006) 499 – 502
Gynecologic Oncology
www.elsevier.com/locate/ygyno

Effectiveness of darbepoetin alfa versus epoetin alfa for the treatment of chemotherapy induced anemia in patients with gynecologic malignancies

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Received 27 July 2005
Available online 10 January 2006

Abstract

Objective. Chemotherapy induced anemia (CIA) commonly occurs in gynecologic oncology patients. This often leads to treatment with erythropoietic stimulating agents in order to prevent chemotherapy delays, dose modifications and transfusion of red blood cells. Our objective was to determine the subsequent transfusion rates following administration of either darbepoetin alfa or epoetin alfa.

Methods. A single institution retrospective chart review was performed utilizing patients from January 2003 to September 2004 who received either darbepoetin alfa or epoetin alfa for CIA (Hgb $\leq$ 10.0). Data collection variables included patient demographics, cancer diagnosis, chemotherapy treatment(s), laboratory data, erythropoeisis stimulation data, and transfusions. Sample size calculations were set to detect a 20% transfusion rate difference between the two groups. Chi-square, Fisher exact test and student *t* tests were used for statistical analysis.

Results. 123 patients were eligible for analysis (60 darbepoetin alfa; 62 epoetin alfa). 93% of darbepoetin alfa patients received 200 mg every other week, while 86% of epoetin alfa patients received 40,000 U weekly. The darbepoetin alfa and epoetin alfa groups were similar in respect to age, race, tumor type, histology, previous chemotherapy, number of chemotherapy agents, weeks of erythropoietic stimulation, and baseline serum levels of creatinine and hemoglobin. The mean baseline Hgb and change in Hgb was similar for each group (darbepoetin alfa = 11.2, 2.5 and epoetin alfa = 11.3, 2.3). Twenty one (35%) of the darbepoetin alfa patients received a transfusion of packed red blood cells compared to 12 (19%) of epoetin alfa patients ($p = 0.05$).

Conclusions. This retrospective analysis powered to detect differences in transfusion rates revealed a statistically significant difference in transfusion rates between darbepoetin alfa and epoetin alfa for the treatment of CIA. These data warrant a randomized prospective trial in gynecologic oncology patients with careful attention to the timing of initiation of treatment, dosing regimens, and titration of growth factor.

Keywords: Chemotherapy induced anemia; Darbepoetin alfa; Epoetin alfa; Transfusion

Introduction

Over eighty-two thousand women in 2005 will be diagnosed with a gynecologic malignancy [1]. For the majority of these patients, chemotherapy is indicated as a crucial part of their treatment regimen. Anemia is a common complication for these patients undergoing treatment with myelosuppressive chemotherapeutic agents. Symptoms of anemia can include lethargy, fatigue, weakness, and dyspnea which in turn can contribute to a decreased quality of life [2]. Furthermore patients, once anemic, often require transfusion of packed red blood cells (PRBCs) which itself is not without risks. A recent study in 2004 found that in treating 2719 patients with solid tumors with chemotherapy, 38% of patients had a hemoglobin less than 11 g/dl and 30% required at least one blood transfusion [3].

Erythropoietin is a hormone produced mainly by the kidney, and in lesser amounts by the liver, that activates red cell production in the bone marrow. Recombinant human erythropoietin (rHuEPO) initially used to treat anemia in patients requiring hemodialysis, is also extensively used and approved for the management of chemotherapy induced anemia (CIA). Normalization of hemoglobin levels to greater than or equal to 10 g/dl has been shown to improve both sense of well being and performance status. Two FDA approved drugs for treatment of CIA include darbepoetin

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doi:10.1016/j.ygyno.2005.11.027

alfa and epoetin alfa. Darbepoetin alfa contains two additional N-linked carbohydrate side chains and up to 8 additional sialic acid residues, thus, resulting in a 3-fold longer half-life than epoetin alfa [2]. This lends itself to more flexibility in dosing schedules.

The efficacy of epoetin alfa and darbepoetin alfa in treating CIA has been evaluated in several randomized controlled trials demonstrating a significant increase in hemoglobin levels, reduction in PRBC transfusions, and increased quality of life [4–6]. Patton et al. in a retrospective cohort study found that darbepoetin alfa in dosages of either 100 μg weekly or 200 μg every other week appeared to be as effective in raising hemoglobin levels as epoetin alfa 40,000 U weekly for CIA in patients with non-myeloid malignancies. They found that the transfusion rate was slightly lower for patients treated with darbepoetin alfa versus epoetin alfa (7% vs. 13.7%) [7]. In this trial, only 11% of these patients were undergoing chemotherapeutic treatment for a gynecologic malignancy. Comparative efficacy of these drugs has yet to be evaluated solely in patients with gynecologic malignancies receiving primarily platinum based chemotherapy. We conducted a retrospective study to compare the difference in transfusion rates in patients undergoing chemotherapy with gynecologic malignancies being treated with either darbepoetin alfa or epoetin alfa.

Materials and methods

Patient identification and study design

A retrospective chart review was conducted at our institution of all patients with a gynecologic malignancy that were treated with either darpepoetin alfa or epoetin alfa for CIA from January 2003 to September 2004. These patients were identified through billing records to have received either darbepoetin alfa or epoetin alfa in the aforementioned time frame and all patients had completed therapy by October of 2004. Sixty darbepoetin alfa and sixty-three epoetin alfa patients were selected for detailed chart review. Data were collected from the time of initiation of hematologic stimulating agent. Inclusion criterion were: patients diagnosed with a gynecologic malignancy (cervical, endometrial, ovarian, or vaginal), patients actively receiving chemotherapy with a least one chemotherapeutic agent in a single outpatient setting, a diagnosis of chemotherapy induced anemia (hemoglobin level less than 10.0 g/dl), and patients must have received at least two dosages of either darbepoetin alfa or epoetin alfa. Exclusion criterion included erythropoietic stimulating agent crossover during chemotherapy regimen, missing or incomplete data, and history of previous hematologic disorder. If different erythropoietic agents were used with different sequential chemotherapy regimens, these patients were not excluded, only if crossover occurred during the same chemotherapeutic cycle. Similarly, if patients received more than one chemotherapy regimen during the study period each regimen and the hematologic stimulating agent used were analyzed separately. Prior to study initiation, approval was obtained by the Institutional Review Board at University of Alabama in Birmingham.

Chemotherapy

Depending on recommended standard therapy for respective gynecologic tissue malignancy, patients in each arm received different chemotherapeutic agents either alone or in combination. The majority of patients, 64%, received platinum based therapy, 54% in the darbepoetin alfa cohort and 70% in the epoetin alfa cohort. In the darbepoetin alfa arm, 48% of patients were receiving first line chemotherapy, 47% were receiving second line chemotherapy and 5% were receiving third or fourth line. Similarly in the epoetin alfa arm, 56% of patients were receiving first line chemotherapy, 41% second line, and 3% third or fourth line (Table 1).

Study drugs and dosages

Once a diagnosis of CIA was made, patients received either darbepoetin alfa or epoetin alfa at the recommended dosages. The majority of patients in the darbepoetin alfa arm received dosages of 200 μg every other week (93%). The remainder received dosages of 100 μg weekly or 300 μg every other week. In the epoetin alfa arm most patients received a dosage of 40,000 Units weekly (86%) with the remainder receiving 60,000 Units weekly (Table 1).

Data collection

Information was collected on patient demographics, tumor type, histology, stage, types and dosages of chemotherapy, number of courses of chemotherapy, and number and dosage of erythropoietic agent used. Laboratory data collection consisted of baseline creatinine and hemoglobin levels as well as nadir hemoglobin levels and change in hemoglobin levels after treatment with each hematologic stimulating agent. The number of blood transfusions and units of PRBC received was also collected. There was not a priori hemoglobin level defined at which a patient was to be transfused, rather this was left to attending discretion based on the patients absolute hemoglobin level, performance status and current symptoms.

Endpoints and study goals

The primary objective of this study was to compare transfusion rates between those patients receiving darbepoetin alfa and those receiving epoetin alfa. Secondary objectives included change in hemoglobin after receiving at least two dosages of each hematologic stimulating agent, and to quantify dosage and frequency of administration of each agent.

Table 1
Baseline demographic data and disease types

	Darboepoetin alfa (Aranesp) $n = 60$	Epoetin alfa (Procrit) $n = 63$	P value
Age, median (years)	62	63	0.75
Tumor type, *n* (%)			0.46
Ovary	51 (85%)	53 (84%)	
Cervix	4 (6%)	2 (3%)	
Endometrial	5 (8%)	4 (6%)	
Vaginal	1 (1%)	3 (5%)	
Chemo courses, mean	6.6	7.1	0.25
Chemo drugs			0.67
Single agent (*n*)	25	23	
Double agent (*n*)	32	33	
Triple agent (*n*)	3	6	
Prior chemotherapy			0.24
None (1st line) (*n*)	27	35	
One (2nd line) (*n*)	27	26	
Two (3rd line) (*n*)	4	2	
Three (4th line) (*n*)	2	0	
Number of drug treatments, mean	5.7	8.1	.001
Drug dosage, *n* (%)			
100 μg/week	1 (2%)		
200 μg QO week	56 (93%)		
300 μg QO week	3 (5%)		
40,000 U week		54 (86%)	
60,000 U week		9 (14%)	
Baseline creatinine, mean	0.8	0.8	
Baseline hemoglobin, mean	11.2 g/dl	11.3 g/dl	