Erythropoietin Reduces Anemia and Transfusions after Chemotherapy with Paclitaxel and Carboplatin

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BACKGROUND. The authors report on anemia observed during preoperative paclitaxel and carboplatin chemotherapy in patients with advanced head and neck carcinoma and discuss how the use of recombinant human erythropoietin (r-HuEPO) ameliorates this anemia, reducing the need for subsequent packed red blood cell (PRBC) transfusions.

METHODS. Response to r-HuEPO was defined as reduced hemoglobin fall during preoperative chemotherapy and reduced transfusion requirements during surgery. Thirty-six patients with advanced head and neck carcinoma were evaluable after treatment with preoperative chemotherapy using paclitaxel and carboplatin. Group 1 was comprised of 14 patients who empirically received r-HuEPO at a dose of 150 U/kg 3 times per week for 3 weeks; in patients deemed nonresponders, the dose was increased to 300 U/kg and 450 U/kg in the subsequent courses. Group 2 was comprised of 22 patients who did not receive r-HuEPO.

RESULTS. During preoperative chemotherapy, the mean hemoglobin fall was 0.5 g/dL in Group 1 ($P = 0.40$). In Group 2 there was a statistically significant mean hemoglobin fall of 3.3 g/dL ($P < 0.0001$). There was also a nonstatistically significant trend toward fewer PRBC transfusions: none of 14 patients (0%) in Group 1 versus 4 of 22 patients (18%) in Group 2 ($P = 0.141$).

CONCLUSIONS. A significant fall in hemoglobin and an increase in the need for transfusions were observed in head and neck carcinoma patients receiving carboplatin and paclitaxel chemotherapy prior to surgery. Empiric r-HuEPO therapy appeared to prevent anemia and reduced the need for PRBC transfusions. ***Cancer* 1997;79:1623–8.** © *1997 American Cancer Society.*

KEYWORDS: head and neck carcinoma, erythropoietin, anemia, paclitaxel, carboplatin, drug-induced.

Paclitaxel (Taxol®) is becoming widely used as a cytotoxic agent for treating cancer. Its major dose-limiting side effects include neuropathy and suppression of hematopoiesis (mostly neutropenia).[1,2] Granulocytopenia can be corrected with the use of recombinant granulocyte-colony stimulating factor or granulocyte-monocyte–colony stimulating factor.[3] Anemia has not been described as a clinically significant side effect with the use of paclitaxel as a single agent.[1,2,4]

Carboplatin (Paraplatin®) suppresses neutrophil, platelet, and erythroid production. Anemia has been described as a frequent complication of therapy with the use of as carboplatin as a single agent requiring transfusions (range, 20–39%) in two early clinical reports.[5,6]

Combination therapy with paclitaxel and carboplatin has been observed to cause anemia. Langer et al., while treating Stage IV lung carcinoma, described Grade 3–4 anemia in 62% of patients by Cycle 5 of paclitaxel as a 24-hour infusion and carboplatin on Day 2 as a

30-minute infusion. Approximately 30% of these patients required packed red blood cell (PRBC) transfusions during chemotherapy.[3]

The authors observed cumulative anemia in patients undergoing preoperative chemotherapy using paclitaxel and carboplatin for the treatment of advanced head and neck carcinoma. Due to the observation that 66% of the first 12 patients undergoing surgery required PRBC transfusions, recombinant human erythropoietin (r-HuEPO) was added empirically in subsequent patients in an attempt to reduce surgical transfusions. The authors report their observations on the use of r-HuEPO to treat this chemotherapy-induced anemia.

PATIENTS AND METHODS

Patients

Included in this analysis were head and neck carcinoma patients treated at Saint Louis University Health Sciences Center on a Phase I nonrandomized trial with preoperative paclitaxel and carboplatin. The objective was organ preservation if the tumors responded. Patients were eligible for entry if they had histologically confirmed advanced head and neck carcinoma (clinical Stage III and IV). They had to be newly diagnosed without any prior therapy and have measurable or evaluable disease.

Additional eligibility criteria included a Zubrod performance status of $\leq$2, serum creatinine $<$ 3 mg/dL, serum bilirubin $<$ 1.5 mg/dL, granulocytes $>$ 1500/μL, platelets $>$ 100,000/μL, a life expectancy of 4 months, and acceptable cardiac function as determined by electrocardiogram. Patients were entered consecutively after informed consent was obtained in accordance with the Institutional Review Board at Saint Louis University Health Sciences Center.

Patient Evaluation

Enrollment required a complete history and physical examination (including laryngoscopy, bronchoscopy, and esophagoscopy) to measure all malignant lesions prior to treatment. Documentation of recent weight loss and biopsy confirmation of carcinoma of the head and neck were required. Additional studies to define the extent of disease and evaluate end-organ function included relevant computerized tomography (CT) of the head and neck, chest X-ray, complete blood count (CBC) with differential and platelet count and multiphasic chemistry profile (sequential multiple analysis 19). Physical examination of indicator lesions was performed every 3 weeks. Repeat CT scans were performed after the second course of chemotherapy and again after the third course.

Laboratory parameters included CBC with differential and platelet count obtained every week during chemotherapy and several times per week during the perioperative interval. Serum erythropoietin levels, iron studies (iron, total iron-binding capacity, and ferritin), serum folic acid, serum B-12, and blood reticulocyte counts were not obtained on the first 9 patients whereas they were obtained on 25 of 28 subsequent patients.

Treatment

Patients were treated with paclitaxel, 150–265 mg/m^2 intravenously (i.v.) on Day 1 over 3 hours. The dose of paclitaxel was escalated in cohorts of patients in a Phase I fashion. Immediately after the paclitaxel infusion, carboplatin was administered i.v. over 1 hour at 7.5 mg/mL/minute according to the formula of Calvert et al. The dose of carboplatin was held constant for all patients. Chemotherapy was administered every 21 days for 2 to 3 courses. After two to three courses primary tumor sites were rebiopsied. If patients were found to be in pathologic complete remission on rebiopsy, radiation was substituted for surgery. Patients with detectable cervical lymph node disease at presentation were treated with a neck dissection before receiving radiation.

In Group 1, r-HuEPO was started on Day 1 of each chemotherapy course, administered at a dose of 150–450 U/kg 3 days a week on Monday, Wednesday, and Friday. The dose during the first course of chemotherapy was 150 U/kg. If the hemoglobin fell $\geq$ 1 g/dL during Course 1, the dose was escalated during Course 2 to 300 U/kg, if the hemoglobin fell $\geq$1 g/dL in course 2, the dose was then escalated in Course 3 to 450 U/kg. This group was treated with simultaneous oral iron and folic acid for the entire duration of their r-HuEPO challenge (ferrous sulfate, 325 mg orally three times daily and folic acid, 2 mg orally each day).

Safety parameters of polycythemia were monitored in the group who received r-HuEPO. r-HuEPO was not initiated if hemoglobin was $\geq$16 g/dL. Once r-HuEPO was initiated, the hemoglobin was checked weekly. If the hemoglobin rose to 18 g/dL, r-HuEPO was stopped until hemoglobin fell to 16g/dL, at which point r-HuEPO was reintroduced. During preoperative chemotherapy, safety parameters for anemia also were observed. If the hemoglobin fell $<$8 g/dL or the patient became symptomatic from anemia, PRBC transfusions were administered. During surgery, transfusions were administered at the discretion of the anesthesiologist depending on the amount of intraoperative blood loss. During the postoperative phase, transfusions were administered to keep hematocrit $>$ 24 unless a free flap reconstruction was performed, in which case the hematocrit was maintained $>$30. The number of units

administered was at the discretion of the treating physician or surgeon.

Statistical Considerations

For purposes of this observational study, outcome variables measured included hemoglobin, change in hemoglobin, transfusion occurrences, and number of units transfused. Pre- and posttreatment hemoglobin values within the two treatment groups were assessed using the paired samples *t* test. The difference in hemoglobin, (pre- and posttreatment) and the number of units transfused between the two groups was assessed using the independent samples *t* test. The change in hemoglobin over time was evaluated by repeated measures of analysis of variance. The Fisher's exact test (two-tail) was used to compare the difference in the rate of transfusion in the two groups. An a priori level of significance of 0.05 was used for all comparisons.

RESULTS

Thirty-seven patients with advanced head and neck carcinoma were treated with preoperative chemotherapy using paclitaxel and carboplatin. No r-HuEPO was used in the first 13 patients. A mean 3.5 g/dL (range, 2.1–5.0 g/dL) fall in hemoglobin was observed in these patients; 54% required PRBC transfusion either preoperatively or at the time of surgery. In the next 9 patients r-HuEPO was empirically added simultaneously with their chemotherapy and a mean fall in hemoglobin of only 0.8 g/dL (range, 0.2–4.8 g/dL) was observed. The subsequent 15 patients were randomized to receive or not receive r-HuEPO. Six patients were randomized to receive r-HuEPO and nine not to receive r-HuEPO. One patient who was randomized not to receive r-HuEPO was excluded from analysis due to early death 12 days after receiving Course 1. Anemia and transfusion data of the remaining 36 patients were combined for analysis in this study. A total of 14 patients were treated with r-HuEPO and 22 were not. Patient characteristics are presented in Table 1.

TABLE 1
Patient Characteristics

Characteristic	No.	r-HuEPO	No r-HuEPO
Patients entered	36	14	22
Histology			
Squamous	34	14	20
Undifferentiated	2	0	2
Stage			
III	6	7	6
IV	30	7	16
Paclitaxel (mg/m^2)			
150	5	0	5
175	3	0	3
200	8	3	5
230	6	5	1
250	8	3	5
265	6	2	4
Age (yrs), median (range)	36	56 (42–68)	58 (17–76)
PS, Karnofsky, median (range)	80 (70–100)	80 (70–100)	80 (70–100)

No.: number of patients; r-HuEPO: recombinant human erythropoietin; PS: performance status.

In the 14 patients who received r-HuEPO, the hemoglobin values before chemotherapy averaged 14.1 g/dL (range, 11.3–15.2 g/dL) and were similar to those after 2 to 3 courses (mean 13.6 g/dL; range, 9.9–16.3 g/dL). The difference was not statistically significant ($P = 0.40$) (Table 2). Five patients were noted to have hemoglobin values < 14.0 g/dL prior to chemotherapy (11.3 g/dL, 12.3 g/dL, 13.3 g/dL, 13.8 g/dL, and 13.9 g/dL, respectively). During preoperative chemotherapy, none of these 14 patients required PRBC transfusion. Eleven patients underwent surgery. Three of these 11 patients (27%) required PRBC transfusion with an average of 1.7 units (range, 1–2 units) (Table 3). Three patients did not undergo surgery because two refused and one was deemed to be inoperable.

In the 22 patients not receiving r-HuEPO, the average hemoglobin before chemotherapy was 14.2 g/dL (range, 12.1–16.5 g/dL). After 2 to 3 courses, the mean hemoglobin fell to 10.9 g/dL (range, 7.4–13.9 g/dL). The difference in pre- and postchemotherapy mean hemoglobin was 3.3 g/dL, which was highly statistically significant ($P < 0.0001$) (Table 2). Five patients were observed to have hemoglobin values < 14.0 g/dL prior to chemotherapy (12.8 g/dL, 12.8 g/dL, 13.6 g/dL, 13.8 g/dL, and 13.9 g/dL, respectively). Four of the 22 patients in this group (18%) required PRBC transfusion during preoperative chemotherapy, each receiving 2 units of PRBC (Table 3). Fifteen patients underwent surgery. Three of these 15 patients were excluded from this part of the analysis. Two required transfusion preoperatively during the chemotherapy phase and therefore were not transfusion naive. Neither of these two patients required PRBC transfusion at the time of their surgery. One was excluded because of a 5-month interval between chemotherapy and surgery during which his hemoglobin rose from 10.3 g/dL to 15.3 g/dL; therefore, at the time of surgery, his hemoglobin did not reflect the suppressive effects of chemotherapy. Twelve patients were transfusion naive at the time of their surgery; 6 (50%) required PRBC transfusion, averaging 3.9 units (range, 2–6 units) each (Table 3). Seven patients were not taken to surgery after preoperative chemotherapy: two refused, three were in pathologic complete remission at the primary

TABLE 2
Preoperative Hemoglobin in Patients Receiving Paclitaxel and Carboplatin Chemotherapy

	No.	Prechemo mean (range) g/dL	Postchemo[a] mean (range) g/dL	Hemoglobin mean change (range) g/dL	*P* value
r-HuEPO	14	14.1 (11.3–15.3)	13.6 (9.9–16.3)	−0.5 (−4.0–+2.7)	0.40
No r-HuEPO	22	14.2 (12.1–16.5)	10.9 (7.4–13.9)	−3.3 (−1.0–−6.6)	<0.0001

No.: number of patients; Prechemo: before chemotherapy; postchemo: after chemotherapy; r-HuEPO: recombinant human erythropoietin.
[a] After two or three courses of chemotherapy.

TABLE 3
Transfusion Requirements

	Patients no.	PRBC Chemo no. (%)	Surgery patients no.	PRBC surgery no. (%)	PRBC units surgery mean (range)
r-HuEPO	14	0 (0)	11	3 (27)	1.7 (1–2)
No r-HuEPO	22	4[a] (18)	12 [b]	6 (50)	3.9 (2–6)
P value		0.141		0.40	

N: number; PRBC: packed red blood cells; Chemo: chemotherapy; r-HuEPO: recombinant human erythropoietin.
[a] Each of four patients received two units packed red blood cells; two patients did not undergo surgery (one refusal and one death).
[b] Fifteen patients underwent surgery; 2 were censored because they received transfusions during the preoperative chemotherapy phase. Neither of the two censored patients required transfusion at the time of their surgery. One was censored because of a 5-month interval between chemotherapy and surgery.

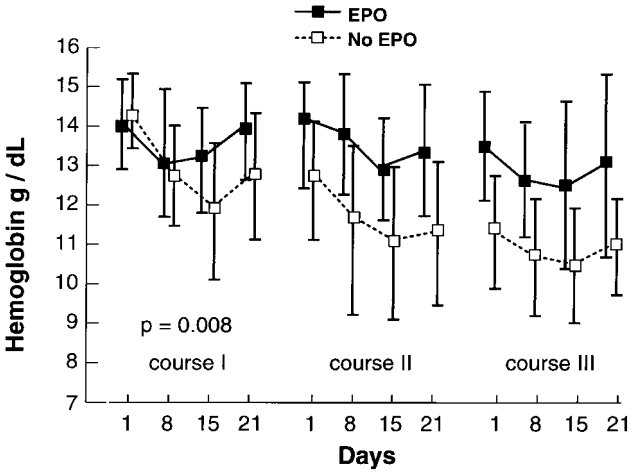

FIGURE 1. Mean hemoglobin difference between 14 patients treated with recombinant human erythropoietin (r-HuEPO) (solid boxes), and 22 patients who did not receive r-HuEPO (open boxes). Error bars: one standard deviation.

tumor site, one was unresectable, and one died of progressive disease during Course 3.

When observations between the two treatment groups were compared, there was a highly significant difference between the baseline and posttreatment hemoglobin after 2 to 3 courses of chemotherapy ($P = 0.000016$). When observed over a period of two courses, using all weekly hemoglobin values obtained, there was a significant drop in hemoglobin over time in the group receiving no r-HuEPO ($P = 0.008$) (Fig. 1). The occurrence of transfusion in those patients not receiving r-HuEPO and patients not receiving r-HuEPO during the chemotherapy phase was not statistically different despite a trend toward fewer transfusions (none in those treated with r-HuEPO vs. 18% in those not treated with r-HuEPO; $P = 0.141$). At the time of surgery, there were fewer transfusions and fewer units PRBC transfused to patients with r-HuEPO administration compared with those receiving no r-HuEPO ($P = 0.40$) (Table 3).

In 25 patients evaluable for baseline serum erythropoietin, there were no significant differences in levels between those 13 patients receiving r-HuEPO (mean, 7.8 mU/mL; range, 2–13 mU/mL) and those 12 patients not receiving r-HuEPO (mean, 9 mU/mL range, 3–23 mU/mL). Likewise, there were no differences in baseline serum values for B-12, folic acid, iron, and iron saturation between the two groups. Some patients in each group were observed to have lower limits of normal levels of serum folate and iron that were not corrected prior to entry on this study. In the 13 patients treated with r-HuEPO, there were no differences in serum values between the responding 8 patients (≤1 g/dL drop in hemoglobin) and 5 nonresponding patients (>1 g/dL drop in hemoglobin) (Table 4). Serial values of serum erythropoietin were obtained at monthly intervals in 7 of 13 patients treated with r-HuEPO. Higher serum erythropoietin values were observed in nonresponders than responders.

DISCUSSION

Trials using single agent paclitaxel to treat cancer have reported conflicting results regarding whether or not ane-

TABLE 4
Serum Erythropoietin and Nutritional Values (25 Patients)

		r-HuEPO N = 13	
Prechemotherapy levels	No r-HuEPO (N = 12)	Nonresponders[a] N = 5	Responders[b] N = 8
Erythropoietin mean (range) mU/mL	9 (3.3–23)	7.2 (2–12)	8.25 (4–13)
B-12 mean (range) pg/mL	615 (218–1217)	418 (289–629)	534 (179–1039)
Folic acid mean (range) ng/mL	6.1 (2.7–13.0)	5.7 (3.3–8.5)	10.7 (4.7–20)
Iron mean (range) μg/dL	49.8 (20–173)	64.6 (11–119)	66.6 (39–121)
Iron saturation % mean (range)	23.6 (9–95)	20.8 (5–41)	22 (14–33)

r-HuEPO: recombinant human erythropoietin.
[a] Hemoglobin >1 g/dL drop.
[b] Hemoglobin <1 g/dL drop.

mia is a major side effect. None of these trials administered r-HuEPO to prevent anemia. Two early Phase I studies in which paclitaxel was administered over 1–6 hours every 3 weeks reported only 1 transfusion after treating a total of 64 patients.[1,2] A third review of the toxicities encountered with use of single agent paclitaxel reported that anemia was rarely induced and that brief neutropenia was the principal toxicity.[4] Researchers in 2 Phase II trials in which treated patients with metastatic breast carcinoma with a 24-hour infusion. The first of these studies reported transfusions were necessary in 12% of patients during the initial 3 courses of chemotherapy.[8] The second reported anemia of Grade 3 and 4 in 18% and 47% of patients, respectively, but did not comment on transfusions.[9] Five reports in which researchers administered 3-hour infusions have generally reported more severe neuropathy and similar degrees of marrow suppression compared with 24-hour schedules. None of these five studies commented on transfusion requirements. The first reported mild and moderate anemia in 45% and 35% of patients, respectively, and severe anemia in $<10\%$.[10] Two reported Grade 3 and 4 anemia (range, 3–12%).[11,12] Two did not comment on the frequency of anemia.[13,14]

Two reports of cancer trials examining natural endogenous erythropoietin during platinum-based chemotherapy observed that endogenous serum erythropoietin rose during platinum-based chemotherapy and that neither pretreatment serum erythropoietin nor starting hemoglobin level predicted which patients would or would not respond to pharmacologic doses of r-HuEPO.[15,16]

Three reports have shown that after exogenous r-HuEPO is simultaneously added with cisplatin combination chemotherapy there is an improvement in the observed anemia. The first observed reduced PRBC transfusions and the second reported anemia would respond to low doses of r-HuEPO.[17,18] The third described hemoglobin rise in a direct dose response to exogenous r-HuEPO.[16]

Two recent reports have described the toxicity of combination paclitaxel and carboplatin chemotherapy. No r-HuEPO was administered in either of these trials. Using a Phase II design, Langer et al. were the first to report anemia after administering paclitaxel, 135–215 mg/m^2 over 24 hours and carboplatin dosed by the formula of Calvert et al. (area under the curve, 7.5). These author treated lung carcinoma patients with 6 courses and observed cumulative anemia of Grade ≥ 2 increasing from 32% during the first cycle to 62% by Cycle 5. Grade 3 or 4 anemia occurred in 33% of the patients of Calvert et al., 30% required PRBC transfusions and, 11% required 20 units of PRBC before the end of 3 cycles, and 26% received 50 units during the last 3 cycles. Approximately 47% of previously irradiated patients required PRBC transfusions, compared with 20% of patients who had not received prior radiation.[3] The second trial was a Phase I report of paclitaxel and carboplatin treatment of patients with advanced ovarian carcinoma. There was no discussion regarding whether or not anemia was observed.[19] Compared with the report by Langer et al.,[3] the authors' observed incidence of Grade 3 and Grade 4 anemia in the 24 patients who did not receive rHuEPO was lower at 13% and 0%, respectively. However, the current trial differed in that all of the patients were newly diagnosed and treatment naive; a shorter infusion schedule of paclitaxel was used, and none of the patients were treated with more than three courses of chemotherapy.

This was a report of the authors' initial observations of anemia and transfusion frequency after paclitaxel and carboplatin chemotherapy. The authors described a group of tumor specific patients in whom r-HuEPO appeared to have a statistically significant effect in preventing anemia when administered simultaneously with chemotherapy. The observations of the current study also showed a nonstatistically significant trend toward fewer transfusions in those patients receiving r-HuEPO. The frequency of transfusions and the number of units PRBC were reduced by 50% in the r-HuEPO group. Due to the small number of patients in the two treatment groups of this uncontrolled study, conclusions regarding the differences noted must be interpreted cautiously. Transfusion data were subject to less precision than the hemoglobin data due to more imprecise endpoints. The patients not receiving preoperative r-HuEPO underwent surgical

resection with a chemotherapy-induced anemia. The decision to transfuse or not to transfuse and the number of units to transfuse was left to the clinical judgement of the attending physician. Due to multiple physicians participating in patient management and interpatient variability, it was difficult to standardize the number of units transfused. A larger trial with more control over the use of transfusions will be needed to confirm these observations. The authors are currently conducting cost analysis on these patients. Their preliminary results suggest therapeutic r-HuEPO is cost-effective in this patient population.[20]

Based on these observations, the authors hypothesize that clinically relevant anemia and transfusion requirements can be reduced in patients receiving carboplatin and paclitaxel chemotherapy plus standard doses of r-HuEPO. They have implemented a randomized trial to confirm this hypothesis.

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