Original Article

Clinical benefits of two different dosing schedules of recombinant human erythropoietin in anemic patients with advanced head and neck cancer

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Summary **A total of 100 patients with stage III or IV head or neck cancer, a performance status of 0-1, and anemia with hemoglobin (Hb) < 10 g/dL at baseline who where to receive chemotherapy concomitantly or sequentially with radiotherapy were randomized to receive either epoetin beta 10,000 IU thrice weekly (TW) (n = 52) and oral iron starting 10-15 days before the start of treatment or epoetin beta 30,000 IU once weekly (OW) (n = 48) and oral iron before the start of treatment. The mean Hb in patients on the thrice weekly (11.96 g/dL) and once weekly (12.50 g/dL) dosing schedules increased significantly (p < 0.01) at the end of the treatment in comparison to respective baseline values of 9.38 g/dL and 9.41 g/dL; levels were 1.2-fold higher, which was significant (p < 0.01), for patients on the once weekly schedule. That said, there was significant improvement (p < 0.01) in mean linear analog scale assessment (LASA) scores for energy level (EL), ability to perform daily activities (AL), and overall quality of life (QOL) for patients on both dosing schedules but these improvements did not differ significantly between schedules (p > 0.05). The 2-year overall survival for patients on both dosing schedules did not differ significantly (p > 0.05). Epoetin beta therapy was found to be equally beneficial and well tolerated for patients on both thrice weekly and once weekly dosing schedules.**

Keywords: Head and neck cancer, anemia, epoetin beta, recombinant human erythropoietin, hemoglobin, quality of life (QOL)

1. Introduction

The worldwide incidence of head and neck cancers exceeds half a million cases and ranks such cancers as the 5th most common malignancies (*1*). New cases of such cancers total approximately 40,000 in the United States annually, accounting for 5% of all adult malignancies. On the Indian sub-continent, such cancers account for more than 25% of all malignancies due to use of cigarettes and chewing tobacco. More than 80% of head and neck malignancies present in locally advanced stages and have a poor prognosis; this has remained unchanged over the past 30 years. The 5-year survival rates of multimodal chemoradiotherapy are below 20%, with a median survival of 12 months or less (*2-4*). Therefore, palliation of symptoms and maintenance of quality of life (QOL) are primary goal of management (*5*).

Anemia is a well-recognized complication of stage IV head and neck cancer and its treatment adversely affects patients' well-being, QOL, and potential survival (*6-11*). Changes in chemotherapy, and particularly the introduction of new agents and treatment regimens, have increased the clinical significance of chemotherapy-related anemia (*9,10*).

Clinical data suggest that even mild to moderate chemotherapy induces anemia, resulting in a perceptible reduction in a patient's energy level, activity level, and overall QOL (*11-14*). Because of the infection and immunosuppressive risks associated with blood transfusions, as well as their transient effect

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on hemoglobin levels and amelioration of anemia, the use of erythropoietic agents has become the new standard of care for patients with chemotherapy-related anemia (*15*). Erythropoietic agents have been associated with decreases in transfusion requirements, higher transfusion-free survival, and significant improvements in QOL as measured by the Functional Assessment of Cancer Therapy-Anemia (FACT-An) and FACT-General (FACT-G) scales (*11*,*16-19*). Recently, erythropoietin has been found to be beneficial in correcting anemia in patients with carcinoma cervix treated with chemoradiotherapy (*20*).

Several randomized trials have compared a once weekly erythropoietin dosage regimen (30,000 IU *s.c.*) with a thrice weekly regimen (10,000 IU *s.c.*) in an effort to establish comparable efficacy between these schedules in patients with chemotherapy-related anemia (*21*,*22*). The investigators reported no significant differences between both groups with regard to changes in hemoglobin (Hb) levels, response rates, or blood transfusion requirements (*21*). The median time to a Hb increase of > 1 g/dL was similar for both the thrice weekly and once weekly regimens (*22*), so less frequent dosing schedules of erythropoietic agents appear to be as effective as the approved regimens.

2. Materials and Methods

2.1. *Patients*

A prospective study was conducted with a total of 100 histologically proven cases of stage III or IV head or neck cancer in patients in apparently good condition who were able to tolerate treatment (Grade 0 or 1 performance status on the World Health Organization (WHO) scale). The patients in question were thoroughly assessed (history, clinical examination, and investigations) and were scheduled to undergo Neoadjuvant 3-cycles paclitaxel and cisplatin chemotherapy at an interval of three weeks followed by concurrent chemoradiotherapy (planned concurrent cisplatin 35 mg/m^2 and conventional radiation dose of 70 Gy in 35 fractions over a period of 7 weeks in external therapy) and epoetin beta 10,000 IU 3 times a week or 30,000 IU once a week.

2.2. *Inclusion criteria*

Inclusion criteria for patients included having histologically proven stage III or IV head or neck cancer, a diagnosis of anemia, a life expectancy of more than 6 months, being in apparently good condition, being able to tolerate treatment, and a performance status of grade 0 or 1. Patients were not to have received any previous definitive treatment (radiotherapy, surgery, chemotherapy, *etc.*) for their disease. Patients with anemia secondary to vitamin deficiency, bleeding, or hemolysis, pregnant or nursing women, and patients undergoing stem-cell transplantation were excluded. Additional significant exclusion criteria were uncontrolled hypertension or cardiac arrhythmia, recent thromboembolism (unless the patient was receiving anticoagulation therapy), untreated brain metastases or seizures, and previous treatment with an erythropoietic agent in the previous 6 months, and anemia attributable to other factors (*e.g.* iron or folate deficiency, hemolysis, and gastrointestinal bleeding).

Eligible patients were randomized into two groups on a once weekly epoetin dosage regimen or on a thrice weekly epoetin dosage regimen; both groups receive epoetin beta along with definitive treatment. Patient randomization was done at a ratio of 1:1 at baseline by the sealed envelope method. This study was approved by this Institution's ethics committee and all participants provided written informed consent before entering the study.

2.3. *Treatment*

On the thrice weekly schedule, the starting epoetin dosage was 10,000 IU administered subcutaneously three times a week for a maximum of 16 weeks. The dosage of epoetin beta was increased to 20,000 IU three times a week if the increase in the Hb level was < 1.0 g/dL after 4 weeks of therapy. If, after an additional 4 weeks of therapy at the higher dosage level, the increase in the Hb level remained < 1.0 g/dL compared to the baseline, then epoetin beta therapy was discontinued. Patients were treated for a maximum of 16 weeks. Patients whose Hb levels exceeded 13 g/dL did not receive further epoetin beta treatment until these levels fell to 12 g/dL, at which time epoetin beta was resumed at 75% of the original dose and titrated to maintain the desired Hb level. The dose of epoetin beta was also reduced if Hb levels increased rapidly (*i.e.*, > 1.3 g/dL in any 2-week period). Patients were transfused based on clinical judgment and Hb < 10 g/dL.

Starting epoetin beta dosage was 30,000 IU administered once weekly by subcutaneous injection. If the increase in the Hb level was < 1.0 g/dL after 4 weeks of therapy, the epoetin beta dosage was increased to 60,000 IU once weekly. If the increase in Hb remained < 1.0 g/dL compared to the baseline after an additional 4 weeks of therapy at the higher dosage level, then epoetin beta therapy was discontinued. Patients were treated for a maximum of 16 weeks. Patients whose Hb levels exceeded 13 g/dL had epoetin beta treatment discontinued until their Hb level fell to 12 g/dL. Treatment with epoetin beta was resumed at 75% of the previous dose and titrated to maintain the desired Hb level. The dose of epoetin beta was also reduced if Hb levels increased rapidly (> 1.3 g/dL in any 2-week period). Patients were transfused based

on clinical judgment and Hb < 10 g/dL. All patients were randomly assigned immediately upon enrollment and were scheduled to receive epoetin over a 16-week treatment period. The drug was administered by a health care provider; self-injection was not permitted, and dose modification was done depending on the Hb level.

2.4. *Evaluations*

Baseline information included patient demographics, weight and blood pressure, tumor histology, current chemotherapy and radiation therapy regimens, Hb level, and transfusion use. Patients were seen and evaluated each month until the completion of treatment. Monthly evaluations included the Hb level, maintenance of the Hb level, transfusion requirements since the last study visit, adverse events, and improvement in overall QOL, which was rated by patients using a 100-mm linear analog scale assessment (LASA) that rated energy level, ability to perform daily activities, and overall QOL. LASA assessment done by placing vertical marks on each line of a 100-mm linear analog scale to indicate the patient's answers regarding his or her energy level, ability to perform daily activities, *i.e.*, activity level, and overall QOL. LASA was performed at baseline, *i.e.*, before starting the first cycle of chemotherapy. Improvements in LASA were assessed gradually at the completion of each cycle of chemotherapy and during and at the completion of chemoradiotherapy for both groups of patients on the thrice weekly and once weekly epoetin dosage regimens. Tumor response was classified according to the WHO criteria (*23*). Adverse events were monitored and graded using the National Cancer Institute Common Toxicity Criteria version 2.0 (*24*).

2.5. *Statistics*

Changes in the mean levels of Hb, energy level, activity level, and overall QOL from baseline to the end of treatment for patients on both schedules were assessed with a two sample paired *t*-test while the mean differences in those indices for patients on the two schedules were determined with a two sample unpaired *t*-test. Categorical data were compared with Fisher's exact test, a χ^2 test, and a proportion Z-test. Cumulative survival rates for patients on both schedules were calculated using Kaplan-Meier's method and the difference between survival rates was evaluated with a log-rank test. The power of the effect size was evaluated according to Cohen (*25*). The power of the effect size, as measured by a two-sided *t* test with a 5% type I error rate, was predicted to have 80% power to detect a difference of 0.29 in Hb for patients on the two dosing schedules with a 95% CI for 95 subjects in total.

A two-tailed ($\alpha = 2$) probability value of $p < 0.05$ was considered to be significant. MS EXCEL (MS Office 1997-2003) and GraphPad Prism (version 5) were used for analysis.

3. Results

One hundred patients in total were enrolled in the study, of which 52 were randomly selected to receive epoetin beta 10,000 IU thrice weekly and 48 were randomly selected to receive epoetin beta 30,000 IU once weekly; both groups received epoetin beta along with definitive treatment. The once weekly dosage group had 45 evaluable patients in total (3 patients withdrew before the start of treatment) and the thrice weekly dosage group had 50 such patients (2 patient withdrew before the start of treatment).

The baseline characteristics of subjects on the two dosing schedules are summarized in Table 1. Comparison indicated that the baseline characteristics for patients on the two dosing schedules did not differ significantly, *i.e.*, statistically they were found to be the same.

The levels of Hb, energy level, activity level, and overall QOL at baseline, at the end of the treatment, and changes from baseline to end of treatment for patients on the two dosing schedules are summarized in Table 2. At baseline, at the end of treatment, and changes in the mean level of Hb, energy level, activity level, and overall QOL did not differ significantly ($p > 0.05$) for patients on the two dosing schedules, except for changes in Hb, which were significantly higher ($p < 0.01$) for patients on the once weekly schedule (Table 2). The changes (improvement) in Hb, energy level, activity level, and overall QOL for patients on both dosing schedules were found to be significantly higher ($p < 0.01$) at end of the treatment in comparison to the respective baseline values (Table 2).

The improvement in Hb, energy level, activity level, and overall QOL for patients on the two dosing schedules is summarized in Table 3. The improvement in Hb, energy level, activity level, and overall QOL for patients on the thrice weekly dosing schedule was found to be 2.57, 40.26, 30.29, and 23.84 g/dL, respectively, while the improvement for patients on the once weekly dosing schedule was 3.13, 40.68, 30.63,

Table 1. Baseline characteristics of patients on two different dosing schedules

Characteristics	Once weekly	Thrice weekly
Total patients registered (*n*)	48	52
Mean age (yrs)	48.18 (45-72)	48.27 (43-70)
Histology		
Squamous	46	49
Unspecified	2	3
Stage		
III	24	25
IV	24	27
Mean hemoglobin (g/dL)	9.41 (9-10)	9.38 (9-10)

Values in parentheses indicate the range.

Table 2. Statistics (Mean ± S.D.) on outcome variables for patients on two different dosing schedules

Variables	Treatments	Initial (baseline)	Final (end of CRT)	Change (Final – Initial)
Hb	OW	$9.41 \pm 0.43_{(48)}$	$12.50 \pm 0.49_{(45)}$	$3.13 \pm 0.41_{(45)}^{**}$
	TW	$9.38 \pm 0.39_{(52)}$	$11.96 \pm 0.46_{(50)}$	$2.57 \pm 0.53_{(50)}^{**}$
	t (OW *vs.* TW)	0.26^{ns}	5.59^{**}	5.67^{**}
EL	OW	$34.50 \pm 0.71_{(48)}$	$75.18 \pm 0.75_{(45)}$	$40.68 \pm 0.83_{(45)}^{**}$
	TW	$34.15 \pm 1.78_{(52)}$	$74.46 \pm 2.71_{(50)}$	$40.26 \pm 3.39_{(50)}^{**}$
	t (OW *vs.* TW)	1.26^{ns}	1.72^{ns}	0.81^{ns}
AL	OW	$36.55 \pm 0.72_{(48)}$	$67.11 \pm 0.71_{(45)}$	$30.63 \pm 0.88_{(45)}^{**}$
	TW	$36.38 \pm 0.69_{(52)}$	$66.64 \pm 1.91_{(50)}$	$30.29 \pm 1.93_{(50)}^{**}$
	t (OW *vs.* TW)	1.26^{ns}	1.56^{ns}	1.09^{ns}
QOL	OW	$42.19 \pm 0.73_{(48)}$	$66.44 \pm 0.62_{(45)}$	$24.30 \pm 0.78_{(45)}^{**}$
	TW	$42.10 \pm 1.50_{(52)}$	$65.94 \pm 2.00_{(50)}$	$23.84 \pm 2.48_{(50)}^{**}$
	t (OW *vs.* TW)	0.38^{ns}	1.62^{ns}	1.19^{ns}

^{ns} $p > 0.05$; ** $p < 0.01$; Data expressed as mean ± S.D. The numbers in parentheses indicate the number of patients.
Abbreviations: Hb, hemoglobin; EL, energy level; AL, activity level; QOL, overall quality of life; OW, once weekly; TW, thrice weekly; CRT, chemoradiotherapy.

and 24.30 g/dL, respectively. The net improvement in Hb, energy level, activity level, and overall QOL was respectively 1.2, 1.0, 1.0, and 1.0-fold higher for patients on the once weekly schedule, but none of these improvements were statistically significant ($p > 0.05$) except for improvement in Hb.

The mean time to an increase in Hb of > 1 g/dL was 4.2 and 4.4 weeks for patients on the thrice weekly and once weekly dosage regimen, respectively, although the difference was not statistically significant. The mean target Hb level of > 12 g/dL and maintenance of Hb between 11.96 g/dL to 12.50 g/dL was achieved in 64.9% and 65.5% of the thrice weekly and once weekly group, respectively.

The response rate, 2-year survival, disease-free survival, and reduction in blood transfusions for patients on the two dosing schedules are summarized in Table 4. The number of blood transfusions did not differ significantly ($p > 0.05$) for patients on a thrice weekly (54%) or once weekly (53%) schedule. Similarly, the reduction in blood transfusions did not differ significantly ($p > 0.05$) for patients on a once weekly (46%) and thrice weekly (46%) schedule. The one-month overall response rate, 2-year overall median survival (Figure 1), disease-free survival, and survival rate for patients on the two dosing schedules did not differ significantly, either ($p > 0.05$). The incidence of acute toxicity was similar for patients on both treatment schedules (Table 5). There were no adverse events related to epoetin beta in either of the treatment groups.

4. Discussion

Despite the potential benefits of erythropoietic agents in cancer-associated anemia, less than one half of eligible persons currently receive therapy with these drugs (*26*). Many factors may contribute to this putative underuse, including cost factors and US Food and Drug administration-approved schedules, as frequent doses

Table 3. Improvement (% mean change) in outcome variables for patients on two different dosing schedules

Variables	Once weekly (%)	Thrice weekly (%)	Net improvement (Once weekly/Thrice weekly)
Hb	32.9	27.4	1.2^{*}
EL	117.9	118.0	1.0^{ns}
AL	83.6	83.2	1.0^{ns}
QOL	57.5	56.6	1.0^{ns}

Abbreviations: Hb, hemoglobin; EL, energy level; AL, activity level; QOL, overall quality of life; OW, once weekly; TW, thrice weekly; ^{ns} $p > 0.05$; * $p < 0.05$.

Table 4. Response rate and prognosis for patients on two different dosing schedules

Characteristics	Once weekly	Thrice weekly
Total patients evaluated (*n*)	45	50
Blood transfusion (*n*)	24	27
One-month overall response rate (%)	93	96
2-year overall median survival (months)	23	20
2-year disease-free survival (%)	60	62
2-year survival rate (%)	52	58
Reduction in blood transfusions (%)	46	46

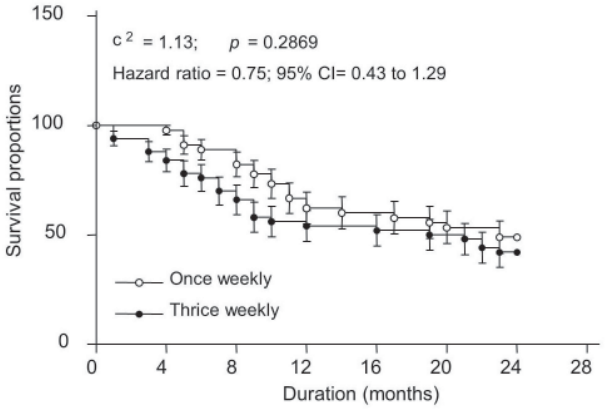

Figure 1. Cumulative survival proportions (%) for patients on two different dosing schedules with standard error (vertical bar).

Table 5. Grade-wise acute and late toxicity (%) for patients on two different dosing schedules

Toxicity	Once weekly				Thrice weekly			
	Grade 1 toxicity (G1)	Grade 2 toxicity (G2)	Grade 3 toxicity (G3)	Grade 4 toxicity (G4)	Grade 1 toxicity (G1)	Grade 2 toxicity (G2)	Grade 3 toxicity (G3)	Grade 4 toxicity (G4)
Acute								
Skin	100	94	30	0	100	92	32	0
Mucositis	100	98	39	4	100	98	40	4
Stomatitis	100	98	35	4	100	97	45	4
Chewing and Eating	100	98	69	3	100	98	69	4
Xerostomia	95	97	45	5	96	96	39	4
Dysphagia	79	69	26	4	79	69	26	4
Dysgeusia	93	59	32	0	90	56	30	0
Anorexia	85.6	86.7	35	4	86	87	34	4
Nausea	87	85	36	3	87	85	34	4
Hematological	20	18	8	0	22	16	7	0
Infection	15	10	2	0	14	8	1	0
Late								
Radiation necrosis	2	1	1	1	2	2	1	0
Chronic xerostomia	76	73	42	4	75	70	30	3
Loss of taste	49	33	29	0	49	30	29	0
Tooth decay	30	28	4	0	29	26	3	0

are required to get the desired results, *e.g.* in a recent summary of trials including patients with solid tumors, epoetin beta (100-200 IU/kg *s.c.* thrice weekly) elicited mean Hb increases of 0.89-2.7 g/dL from baseline to last assessment, in durations ranging from 8 to 24 weeks (*16*).

Epoetin beta is also associated with decreases in transfusion requirements of 37-90% compared with no treatment (*16*). In a randomized, double-blind, placebo-controlled trial that enrolled 349 patients with transfusion-dependent hematologic malignancies, epoetin beta 150 IU/kg *s.c.* thrice weekly improved hematologic parameters and QOL (*19*). Since a thrice weekly dosage schedule is inconvenient for the patient and physician alike, a once weekly epoetin beta dosage was recently compared with the thrice weekly regimen in an effort to establish comparable efficacy between these schedules in patients with chemotherapy-related anemia.

In an open-label trial, 241 patients with lymphoproliferative malignancies with baseline Hb 9-11 g/dL and low serum erythropoietin levels (< 100 Mu/mL) were randomly selected to receive epoetin beta 10,000 IU *s.c.* thrice weekly or 30,000 IU *s.c.* once weekly (*21*). The investigators reported no significant differences between groups regarding changes in Hb levels, response rates, or blood transfusion requirements (*21*). The median time to Hb increase of > 1 g/dL was similar for patients on both the thrice weekly and once weekly regimens (*22*). The authors concluded that epoetin beta administered once weekly is an effective and convenient treatment for anemia in patients with lymphoproliferative malignancies and defective endogenous erythropoietin production (*21*).

The results of the current study are very similar to those reported in the literature indicating that once weekly and thrice weekly regimens of epoetin beta have comparable efficacy, *i.e.*, the increase in Hb levels, decreased transfusion requirements, improved functional status, overall QOL, and safety profiles of the thrice weekly and once weekly dosing schedules appear to be similar for anemic patients with cancer of the head and neck who were receiving radiotherapy concomitantly or sequentially with chemotherapy. In addition, a once weekly dosing schedule is more convenient for patients and physicians alike.

5. Conclusion

Erythropoietic agents have a well-established efficacy for treating chemoradiotherapy-related anemia in head and neck cancer, leading to statistically significant improvements in hematologic parameters, QOL, and decreased transfusion requirements. Once weekly and thrice weekly epoetin beta regimens exhibit similar efficacy and safety profiles in patients with head and neck cancer who are receiving chemoradiotherapy. Therefore, a once weekly dosage regimen appears to be as effective as approved regimens and offer greater convenience for patients and clinicians.

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