

ORIGINAL ARTICLE

A Randomised Comparison of Darbepoetin alfa with Epoetin for Chemotherapy Induced Anaemia in Nonhaematological Tumours

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ABSTRACT

BACKGROUND: Although once weekly (QW) Darbepoetin is nowadays used by many for chemotherapy induced anaemia, a head to head comparison with thrice weekly (TIW) Epoetin regimen has not been published so far.

PATIENTS AND METHODS: We randomly compared weekly (QW) darbepoetin alfa with thrice weekly (TIW) Epoetin in 50 cancer patients with chemotherapy induced anaemia ($Hb \leq 11gr\%$). In Group A, Epoetin was administered at 10.000 U TIW (20.000 U in non-responders after 4 weeks). In Group B, Darbepoetin alfa was administered at 150mcg QW (300 mcg as above). Evaluation, including QOL assessment using FACT-An scale, was performed on week 4 and 8.

RESULTS: In group A, Hb increased from 9.81 ± 1.02 at baseline to 10.59 ± 1.38 at 4 weeks ($p=0.007$) and to 11.4 ± 1.99 at 8 weeks ($p=0.001$). It also increased between week 4 and 8 ($p=0.011$). In group B, Hb increased from 10.2 ± 0.87 at baseline to 10.8 ± 1.93 at 4 weeks ($p=0.075$) and to 11.57 ± 2.26 at 8 weeks ($p=0.005$) without significant increase between week 4 and 8 ($p=0.08$). In all 50 patients, Hb increased from 10.01 ± 0.97 at baseline to 10.75 ± 1.69 at 4 weeks ($p=0.003$) and to 11.49 ± 2.11 at 8 weeks ($p=0.000$). It also increased from 10.84 ± 1.74 to 11.49 ± 2.11 ($p=0.003$) between week 4 and 8. Twelve of 25 patients (48%) in group A had to double the Epoetin dose versus 13 (52%) in group B ($P=NS$). Three patients in group A required transfusions compared with 4 in group B ($p=NS$). On an intent-to-treat analysis: RR, at 4 weeks, was 44% for Epoetin versus 44% for Darbepoetin ($p=NS$). At 8 weeks, it was 48% and 60%, respectively ($p=NS$). QOL analysis unexpectedly showed that fatigue and emotional scores were worse in Group B than in Group A. Whether this, not easily explainable observation, is just an incidental finding remains to be shown in larger series.

CONCLUSIONS: QW Darbepoetin is a convenient therapy and it induced haemoglobin changes of similar magnitude to TIW Epoetin.

KEY WORDS: Supportive care, fatigue, transfusions, cancer

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INTRODUCTION

The incidence of anaemia in cancer patients receiving chemotherapy varies between 35% and 95%, depending upon the tumor type, timing and chemotherapeutic regimen used [1-3]. There is an increasing understanding of the symptoms of anaemia and their impact on the lives of patients with cancer. Furthermore, anaemia has been recognized as a poor prognostic factor for survival in many malignancies [4-6].

Recombinant human erythropoietin (Epoetin) is effective in treating chemotherapy induced anaemia and its effectiveness in improving quality of life and fatigue level has been confirmed in a randomized, placebo-controlled clinical trial [7]. The recommended starting regimen is 150U/Kg or a fixed dose of 10.000 U given subcutaneously, thrice weekly (TIW), which can be increased to 20.000 U thrice weekly if no response in haemoglobin level is observed after 4 weeks of treatment.

Despite the logic in using erythropoietic therapy for cancer related anaemia, there is evidence that not infrequently anaemic patients do not receive Epoetin until their haemoglobin level has dropped as low as 9 g/dl [8]. This current low rate of treatment with Epoetin is due to several factors including cost of therapy, lack of perception of the importance of anaemia by many oncologists and the relatively high degree of non response to therapy. The inconvenience of the indicated administration schedule for Epoetin might be another factor.

Recently, a less frequent dosing of Epoetin, namely once-weekly, has been found to be effective therapy although an increase in the dose by 33% compared with the registered dosing recommendations was required [9]. These results have led many oncologists in Europe and USA to adopt the weekly schedule in their clinical practice.

Darbepoetin alfa, a recombinant product characterized by the presence of two additional carbohydrate side chains, although it stimulates erythropoiesis by the same mechanism as endogenous erythropoietin and Epoetin, it demonstrates an extended half life in the body [10]. Despite the fact that the additional N-glycosylation results in a lower receptor binding capacity and a lower *in vitro* biological activity [11], Darbepoetin alfa demonstrates a greater *in vivo* biological activity than Epoetin [10,11].

There is now enough evidence that once-weekly (QW) administration of Darbepoetin is an effective treatment of chemotherapy induced anaemia [12-14]. The scheme has been recently used by many oncologists [15,16] nevertheless a head to head comparison with TIW Epoetin regimen has not been published so far.

We, therefore, decided to compare, in a prospective

randomized study, the effectiveness of QW Darbepoetin alfa with TIW Epoetin.

STUDY AIM

In the present study, we aimed to randomly compare the overall effectiveness of QW with TIW Epoetin. To achieve this purpose we set out:

- To compare the magnitude of haemoglobin changes from baseline to weeks 4 and 8, between patients treated with Darbepoetin alfa and those treated with Epoetin;
- To compare the needs for red blood cell transfusion, during chemotherapy, between the two groups of patients;
- To compare the impact of the two erythropoietins on the quality of life of the patients;

PATIENTS AND METHODS

Patients: Inclusion and Exclusion criteria are shown in table 1.

Laboratory investigations: Detailed pre-randomisation tests performed in all eligible patients and follow-up investigations are included in table 2.

STUDY DESIGN AND STUDY DRUGS

This was a phase III, open-label study in which eligible patients were randomized in two groups:

Group A Patients received Epoetin 10.000 U thrice weekly. If an increase in Hb of ≥ 1.5 gr/dl was not observed after 4 weeks, the dose was increased up to 20.000 U. If a < 1.5 gr/dl increase was observed after 4 weeks of titrating up the dose, Epoetin was discontinued.

Group B Patients received Darbepoetin alfa 150 mcg once weekly. If an increase in hemoglobin ≥ 1.5 gr/dl was not observed after 4 weeks, the dose was increased up to 300mcg. If a < 1.5 gr/dl increase was observed after 4 weeks of titrating up the dose, Darbepoetin was discontinued.

In both groups, when Hb reached the level of 13.5 gr/dl,

TABLE 1. Inclusion and Exclusion criteria

Inclusion criteria	Exclusion criteria
- Age ≥ 18 years	- Iron, B ₁₂ or Folate deficiency
- Solid tumours only	- Bleeding or haemolysis
- Life expectancy of ≥ 4 months	- Serum ferritin ≤ 10 ng/ml
- Scheduled to receive cyclic chemotherapy for at least 12 weeks	- More than two RBC transfusions within 4 wks of randomisation or any within 16 days
- Hb level of 11gr/dl or less	- Epoetin therapy within 8 weeks
- Decrease of Hb ≥ 1.5 gr /dl during chemotherapy	- Uncontrolled hypertension
- ECOG 0-3	- Active infection
- Serum creatinine ≤ 2 mg/dl	

TABLE 2. Detailed pre-randomisation tests and follow-up investigations

Pre-randomisation tests	Follow-up tests
1. Complete blood count and review of peripheral blood smear	1. Complete blood count was performed before each course of chemotherapy and in weeks 4 and 8
2. Serum creatinine	2. Serum iron level was estimated every 3 weeks
3. Serum Folate level and B ₁₂ level	3. Serum ferritin was estimated every 3 weeks
4. Serum iron level and ferritin concentration	
5. Serum LDH, bilirubin and reticulocyte count for evidence of haemolysis	
6. Bone marrow examination if there was a suspicion of tumour infiltration	

the dose of erythropoetin was titrated as follows: for Darbepoetin, the effective weekly dose was given every two weeks, whereas for Epoetin the effective thrice weekly dose was given once weekly.

In both groups, patients with a ferritin level <20ng/ml received oral iron supplementation.

Red blood cell transfusion was allowed at any time during chemotherapy if Hb dropped to 8.5 gr/dl.

EFFICACY ASSESSMENT

Evaluation was performed at weeks 4 and 8. The following end points were assessed:

1. HAEMOGLOBIN RESPONSE:

Complete response was defined as an increase in H β of ≥ 1.5 gr/dl over baseline in the absence of blood transfusion in the preceding 28 days.

Partial response was defined as an increase between 1 gr/dl and 1.4 gr/dl.

No response was defined as no increase or an increase of <1 gr/dl.

2. CHANGES IN HAEMOGLOBIN LEVEL ON WEEK 4 AND WEEK 8

3. QUALITY OF LIFE:

The FACT-An questionnaire was completed by the patients at baseline, week 4 and week 8.

STATISTICAL CONSIDERATIONS

Analysis was performed on an intent-to-treat basis, and included all patients who received at least one dose of the study drug.

Changes in H β level are expressed as a mean \pm SD. Comparison of the means was performed using the Paired-Samples T test.

Comparative analysis of Hb response rate to erythropoetic therapy between groups was performed using Pearson Chi-

square test. The same test was used in comparing the needs for blood transfusions and of doubling the dose of erythropoetin during the study period.

The impact of haemoglobin changes on quality of life was studied using the Functional Assessment of Cancer Therapy-Anaemia (FACT-An) scale [16]. The FACT-An scale is composed of the FACT-F plus seven additional non-fatigue items. The FACT-F is composed of the FACT-G (physical, emotional, social and functional well-being) plus the Fatigue subscale. Data were initially analysed to determine internal consistency (Cronbach's alfa) and test-retest reliability (inter-class correlation coefficient). Then a 2x3 univariate analysis of variance (ANOVA) was carried out to assess group and time differences as well as group by time interactions, i.e. group differences depending on time.

All analyses were carried out in SPSS v 11.0

ETHICAL CONSIDERATIONS

The study protocol was approved by the Ethics Committee of our hospital.

Patients participating in the study were asked to complete a written consent after having been fully informed about the nature and the aims of the study.

RESULTS

Between September 2003 and March 2004, 50 patients were equally randomized in group A and group B. Their clinical and laboratory characteristics are shown in table 3. Sex, age, stage and PS did not differ significantly in the two groups. Mean Hb was 9.81 gr/dl \pm 1.02 (\pm SD) in group A and 10.2 gr/dl \pm 0.87 (\pm SD) in group B (p=NS). Mean serum ferritin level was 202 ng/ml \pm 142 (\pm SD) in group A and 390 ng/ml \pm 551 (\pm SD) in group B (p=NS).

1. HAEMOGLOBIN RESPONSE:

Total Response (TR) and Complete Response (CR) rates after 4 and 8 weeks of erythropoetic treatment are separately shown for Darbepoetin alfa and Epoetin in table 4. At 4 weeks,

TABLE 3. Clinical and laboratory characteristics of the 50 eligible patients included in the study.

Characteristics	rHuEPO	Darbepoetin
	No (%)	No (%)
Age (years)	61	65
median (range)	(44-76)	(47-76)
Sex (Female)	11 (22)	12 (20)
Disease		
Breast	2 (8)	1 (4)
colon	6 (24)	5 (10)
lung	14 (56)	9 (36)
ovarian	1 (4)	5 (20)
stomach	2 (8)	1 (4)
various	-	4 (16)
Stage		
II	-	2 (4)
III	6 (24)	9 (36)
IV	19 (76)	14 (56)
ECOG		
0 - 1	17 (68)	13 (52)
2	7 (28)	9 (36)
3	1 (4)	3 (12)
Haemoglobin (g%)		
Mean ±SD	9,81 ± 1,02	10.2 ± 0,87
Ferritin (ng/ml)		
Mean ±SD	202 ± 142	390 ± 551

there was an identical TR rate in both groups of patients and a higher but not significant (p=NS) CR with Darbepoetin alfa. At week 8, CR rate was identical for both Epoetin and

Darbepoetin alfa.

In 7 out of 14 (50%) responding patients, Epoetin dose had to be doubled as opposed to 7 out of 15 (47%) responders with Darbepoetin alfa (p=NS).

The needs for blood transfusion were similar in both groups (12% in group A versus 16% in group B).

2. CHANGES IN HEMOGLOBIN LEVEL ON WEEK 4 AND WEEK 8:

Changes in Hb level during the study period for each group of patients, as well as for all 50 patients, are shown in table 5. For group A, there was a significant increase in mean Hb both at 4 and 8 weeks (p=.007 and p=.001, respectively). A significant increase (p=.011) was also observed between weeks 4 and 8. For group B, the increase in Hb level was significant (p=.005) in week 8, but not in week 4 (p=.075). Similarly, no significant (p=.08) increase was observed between weeks 4 and 8.

During the study period, 2 out of the 25 (8%) patients on Epoetin and 9 out of the 25 (36%) on Darbepoetin alfa achieved the Hb level of 13.5 g/dl (p=.017), the predefined point for dose titration.

For the whole group of 50 patients, mean Hb level increased significantly after 4 and 8 weeks of treatment (p=.003 and p=.000, respectively). A significant increase (p=.003) was also observed between week 4 and week 8.

3. QUALITY OF LIFE:

Statistical analysis of the QoL findings demonstrated high internal consistency for FACT-G. There was also high degree of test-retest reliability for physical and social

TABLE 4. Haemoglobin response rate to haemopoetic therapy.

Type of response	Week 4		Week 8		Total
	Group A	Group B	Group A	Group B	
	N (%)	N (%)	N (%)	N (%)	
Complete response	7 (28)	8 (32)	11 (44)	11 (44)	22 (44)
		(p=NS)		(p=NS)	
Partial response	4 (16)	3 (12)	1 (4)	4 (16)	5 (10)
		(p=NS)		(p=NS)	
Total response	11 (44)	11 (44)	12 (48)	15 (60)	27 (54)
		(p=NS)		(p=NS)	

TABLE 5. Changes in haemoglobin level for group A, group B and for all 50 patients.

Timing		Group A	Group B	Whole Group
		Mean Hb (SD)	Mean Hb (SD)	Mean HB (SD)
baseline		9.8 (1.04)	10.2 (.87)	10.02 (.87)
		p=.007	p=.075	p=.003
week 4	p=.001	10.6 (1.4)	10.8 (1.9)	10.75 (1.69)
		p=.011	p=.080	p=.003
week 8		11.4 (1.99)	11.6 (2.3)	11.5 (2.12)

well-being, emotional well-being and functional well-being. Regarding the fatigue subscale (11 items), there was high internal consistency as well as high test-retest reliability. The additional non-fatigue subscale showed also good stability but low internal consistency.

Physical well-being: There were no significant ($p=.21$) differences in mean physical well-being score over time between the two groups. The observed differences were constant over time ($p=.62$ for time by group interaction), indicating that groups do not differ significantly over the three assessments (Figure 1).

Social well-being: There were no significant ($p=.49$) differences in mean social well-being score over time between the two groups, and those differences that were observed were constant over time ($p=.99$ for group by time interaction, Figure 2).

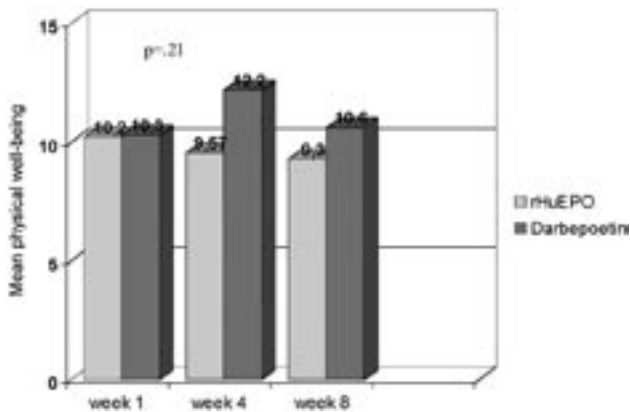


FIGURE 1. Changes in mean physical well-being score during therapy with rHuEPO and Darbepoetin, respectively.

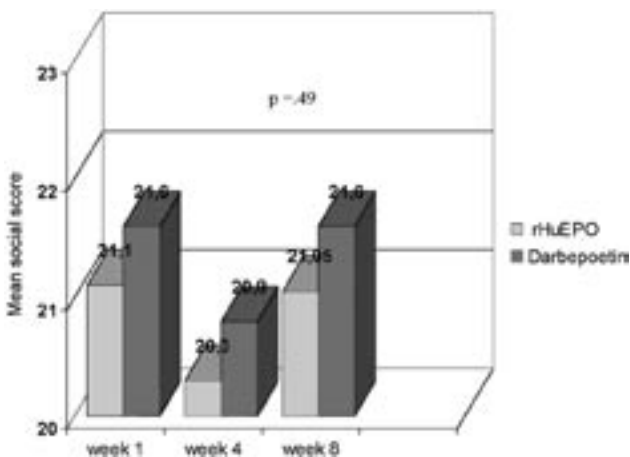


FIGURE 2. Changes in mean social well-being score during therapy with rHuEPO and Darbepoetin, respectively.

Functional well-being: Mean functional well-being score by group over time is shown in figure 3. There were no significant differences in mean functional score between the two groups ($p=.53$) and the observed differences were constant over time ($p=.57$ for time by group interaction).

Emotional well-being: There were significant differences in mean emotional well-being score between the two groups ($p=.016$) in favour of group A. Patients in group B had a tendency for increased emotional scores over time compared with group A ($p=.08$ for time by group interaction), indicating that patients in group B are getting worse over time (Figure 4).

Fatigue subscale: There were significant differences in mean fatigue score between the two groups ($p=.001$), with those in group B having higher fatigue scores than those in

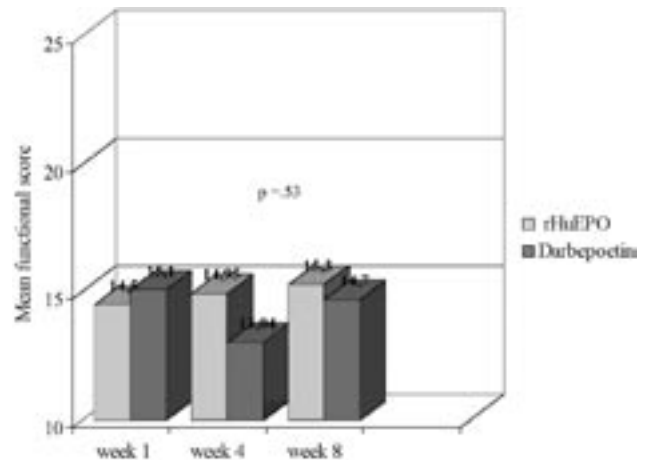


FIGURE 3. Changes in mean functional well-being score during therapy with rHuEPO and Darbepoetin, respectively.

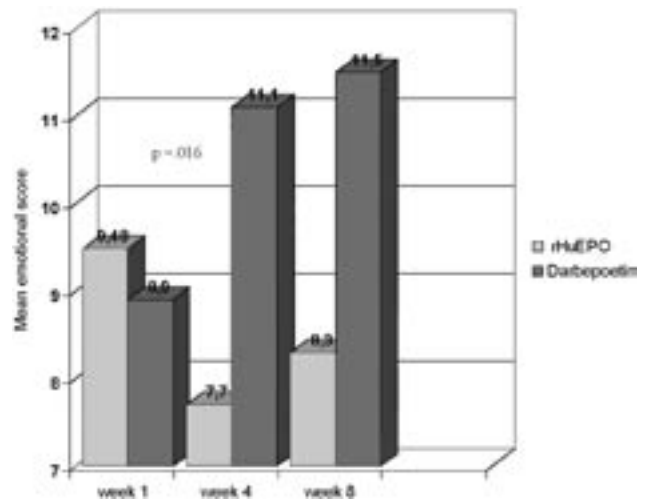


FIGURE 4. Changes in mean emotional well-being score during therapy with rHuEPO and Darbepoetin, respectively.

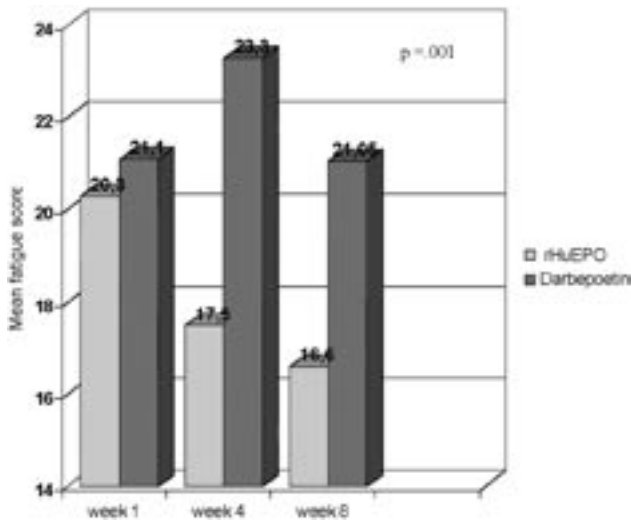


FIGURE 5. Changes in mean fatigue score during therapy with rHuEPO and Darbepoetin, respectively.

group A, indicating that the former group was doing worse than the latter (Figure 5).

Non-fatigue subscale: There were no significant differences in mean non-fatigue score between the two groups ($p=.49$) and the observed differences were similar over time ($p=.89$ for time by group interaction, Figure 6).

DISCUSSION

Although it is considered that QW Darbepoetin alfa is effective for cancer related anaemia [12-14] and this practice

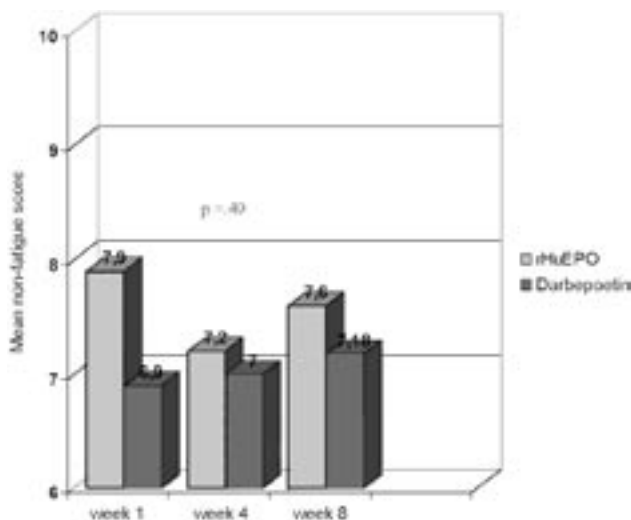


FIGURE 6. Changes in mean non-fatigue score during therapy with rHuEPO and Darbepoetin, respectively.

has been recently adopted by many oncologists [15,16,18], a head to head comparative study of this schedule with TIW Epoetin has not been published so far. From this point of view, we consider that the publication of our findings, although still based on a rather small number of patients, is warranted. The two groups of patients we studied are well defined, doses and schedules of Epoetin and Darbepoetin alfa are those recommended in clinical practice and, most importantly, the assessment of the impact of the erythropoietins on the quality of life of the patients is based on the completion of the FACT-An questionnaire by an exceptional 96% of patients at baseline, 98% at week 4 and 97% at week 8 of treatment.

We found that, on the whole, the administration of erythropoietic treatment was associated with a significant increase in Hb level after 4 weeks of treatment and a highly significant increase after 8 weeks. A significant increase was also observed between week 4 and 8. Nevertheless, when the results were analysed separately for the two groups of patients, the increase remained highly significant after 8 weeks for both erythropoietins but it was significant only for Epoetin after 4 weeks. Likewise, the observed increase in Hb level between week 4 and week 8 was significant only for Epoetin.

On the other hand, TR, PR or CR rates were not significantly different between Epoetin and Darbepoetin alfa at neither 4 nor 8 weeks although, after 8 weeks, there was a trend in favor of Darbepoetin alfa in terms of PR (16% versus 4%) and TR (60% versus 48%). Likewise, during the 8 weeks period, a significantly higher proportion of patients on Darbepoetin alfa (36% versus 8%) reached the predefined titration cut point of 13.5g/dl.

In order to achieve a response, almost half of the patients in each group had to double the dose of erythropoetin during the study period.

Despite the observed significant increase in Hb level, erythropoietic therapy did not obviate the needs for blood transfusion which proved to be similar in both groups of patients. It is worth noting that the 16% requirement for transfusions with the use of Darbepoetin alfa observed in our study is considerably lower than the 27% observed by others [19].

The impact of erythropoietic treatment on the quality of life in terms of physical, social and functional well-being score did not differ between the two groups. Furthermore, the observed, non-significant, differences were similar over time. However, there were significant differences in mean emotional score between the two groups with patients in Darbepoetin alfa group showing a tendency for increased emotional scores over time, indicating that they are getting worse over time. In addition to emotional well-being, there were also significant differences in mean fatigue score between the two groups with those on Darbepoetin alfa having higher fatigue scores, indicating that they are doing worse than patients on Epoetin. It is not easy to explain this rather unexpected observation. It might be due to the more significant increase in mean Hb

at week 4 observed with Epoetin or it might be the play of chance because of the small number of patients. Finally, in terms of non-fatigue score the two groups demonstrated similar behaviour.

We observed no serious adverse reactions with either drug and local pain at the site of injection was not a problem with either Epoetin or Darbepoetin alfa.

CONCLUSIONS

With due caution, because of the small number of patients studied, we conclude that once weekly Darbepoetin alfa seems to be equally effective in ameliorating chemotherapy induced anaemia as thrice weekly Epoetin. However, whether its observed inferiority in terms of fatigue and emotional well-being is an incidental finding and to what degree this would counteract its more convenient administration schedule is not easy to assess at the moment.

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