Erythropoetin β Twice Weekly *Versus* Standard Therapy in Patients with Gynaecological Malignancies – A Randomised Austrian AGO Trial

BIRGIT VOLGGER[1], EDGAR PETRU[2], LUKAS ANGLEITNER-BOUBENIZEK[3], MONIKA WEIGERT[4], ALEXANDER REINTHALLER[5], HARALD LASS[6], ANITA STEMPFL[7], CHRISTIAN GAMPER[8], MARTINA DEIBL[9] and CHRISTIAN MARTH[1]

Department of [1]Obstetrics and Gynaecology, and [9]Medical Statistics, Informatics and Health Economics, Innsbruck Medical University, 6020 Innsbruck;
[2]Department of Obstetrics and Gynaecology, Graz Medical University, 8063 Graz;
[3]Department of Gynaecology, Barmherzige Schwestern Hospital, 4010 Linz;
[4]Department of Gynaecology, Hietzing Hospital, 1130 Lainz;
[5]Department of Obstetrics and Gynaecology, Vienna Medical University, 1090 Vienna;
[6]Department of Gynaecology, Wilhelminen Hospital, 1160 Vienna;
[7]Department of Gynaecology, Paracelsus Medical University Salzburg, 5020 Salzburg;
[8]Department of Gynaecology, Landesklinikum, 2700 Wr. Neustadt, Austria

Abstract. *Background: The influence of two regimens of erythropoetin β on haemoglobin level, quality of life (QoL) and side-effects in patients with gynaecological malignancies was assessed. Patients and Methods: A total of 119 patients during chemotherapy were randomised to either standard therapy with 10,000 IU erythropoetin β three times a week (group A) or 20,000 IU twice a week (group B). Haemoglobin level and QoL were measured. Characteristics of the study population were analysed with descriptive statistical methods. Analysis of variance for repeated measurements was performed with haemoglobin level as dependent variable, and time and study arms as factors. Results: The rise in haemoglobin levels and QoL improvement were significant, without any difference between study arms. Adverse events were similar, except significantly more thromboembolic events in group B (0 vs. 8 events; p=0.003). Conclusion: Our results show similar improvements in haemoglobin level and QoL, but raise the question whether less frequent dosing regimes may result in increased rates of thromboembolic events.*

Correspondence to: Birgit Volgger, MD, Department Obstetrics and Gynaecology, Innsbruck Medical University, Anichstrasse 35, 6020 Innsbruck, Austria. Tel: +43 51250424142, Fax: +43 51250422458, e-mail: birgit.volgger@i-med.ac.at

Key Words: Erythropoetin, thrombosis, gynaecological cancer, breast cancer.

Of all paraneoplastic syndromes, anaemia is one of the most common. The incidence of anaemia varies with tumour type, stage and patient age; up to 40% of cancer patients are anaemic at diagnosis (1, 2), and this frequency increases to 80% following chemotherapy (3).

Tumour hypoxia may contribute to tumour resistance to chemotherapy and radiotherapy (4, 5). Increasing oxygen delivery to tumour tissues may improve response rates and overall survival. Indeed, cancer-associated anaemia was shown to be an independent risk factor for survival regardless of tumour type (6-8). Recombinant erythropoetin promises to provide many of the benefits of blood transfusion and has been widely embraced for this purpose as well as for having an impact on cancer-related fatigue and quality of life (QoL) (9, 10). Recently, however, several clinical trials involving anaemic and nonanaemic cancer patients have raised questions concerning the safety of recombinant erythropoetin with respect to its potential for tumour promotion (11, 12) and pro-thrombotic activity (11, 13, 14).

When the current study was planned in 2001, standard erythropoetin therapy was either subcutaneous or intravenous administration of 10,000 IU of recombinant human erythropoetin three times a week as originally established in the treatment of anaemia associated with renal failure. The purpose of the current study was to compare various weekly erythropoetin dosages and schedules because standard therapy is often inconvenient for outpatients receiving chemotherapy and to assess the influence of two regimens of erythropoetin beta (β) on haemoglobin (Hb) level, QoL, transfusion requirements and safety.

Patients and Methods

Study objectives. The primary objective of our study was to compare two different dosing schedules of erythropoetin β, (NeoRecormon®; Hoffmann-La Roche Ltd, Basel, Switzerland) namely 10,000 IU three times a week (group A) *versus* 20,000 IU twice a week (group B) in patients with anaemia (Hb <11.5g/dL) and the diagnosis of a gynaecological or breast cancer. Secondary objectives included assessment of response rates, transfusion rates and QoL in both study groups. Additional efficacy variables included changes in Hb from baseline to study completion as well as haematocrit, erythrocyte and reticulocyte count, response rate and number of red blood cell (RBC) transfusions.

Patients and study design. This open-label, randomised study was conducted at 11 sites in Austria. Study protocol and amendments were reviewed by independent ethics committees. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines. All patients provided written consent for study participation. The study was conducted between June 2002 and May 2004.

Patients ≥18 years of age who provided written informed consent were enrolled if they met the following criteria: confirmed diagnosis of a gynaecological malignancy including breast cancer, receiving chemo- or radiotherapy, at least two cycles of chemotherapy outstanding, Hb≤11.5 g/dl, platelets between 25 and 500×10^3/l, Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2 and a life expectancy ≥6 months. Patients were excluded if their anaemia resulted from factors other than cancer or its treatment, if they had a history of thrombovascular events (TVEs), uncontrolled hypertension, serious hepatic or renal insufficiency, epileptic disease, phenylketonuria or were pregnant. Patients were also ineligible if they had received RBC transfusions within one week before starting erythropoetin therapy.

Eligible patients were assigned at random to receive 10,000 IU erythropoetin β subcutaneously (*s.c.*) three times (group A) or 20,000 IU erythropoetin β twice a week (group B). Randomisation was stratified by centre, grade of anaemia (mild, Hb 10.1 g/dl-11.5 g/dl; moderate, Hb 8.1-10 g/dl; severe, Hb≤8 g/dl) and tumour progression. Response was defined as an increase in haemoglobin (Hb) of >2 g/dl *versus* baseline or Hb>12 g/dl after therapy.

Erythropoetin β dose was adjusted as follows: At a Hb level ≥12 g/dl dose was reduced to 20,000 IU erythropoetin β/week and discontinued at a Hb level ≥14 g/dl until Hb was ≤12 g/dl again. Further therapy was reduced to 50% of initial therapy. The dose was also reduced to 50% if Hb increased more than 2 g/dl within the first four weeks of erythropoetin therapy. If response to erythropoetin therapy was insufficient, *e.g.* RBC transfusion was needed, Hb level <8 g/dl or Hb increased by <1 g/dl, the dose was raised to 60,000 IU/week. Oral iron supplementation was recommended if transferrin saturation was less than 20%. RBC transfusions were allowed when clinically indicated, but recommended below a value of Hb<8 g/dl.

Study assessments. At baseline, a complete physical examination and clinical laboratory tests were performed and ECOG performance status was recorded. After one to two weeks of therapy, an additional complete blood count (CBC) was taken. After each cycle of chemotherapy, CBC was obtained and administered RBC transfusions, details of chemotherapy (medication, dosing and frequency), antihypertensive therapy, iron supplementation and adverse events were recorded. These data were also collected at study completion after six to eight weeks. Data on QoL were collected using the standardized FACT (Functional Assessment of Cancer Therapy) questionnaire, which comprises a general scale (FACT-G; 27 questions) and an additional anaemia + fatigue module (FACT-AN; 20 questions). Patients were asked to answer the questions at baseline, after three to four weeks of therapy and at study end. Safety was evaluated by continous AE reporting throughout the study and regular evaluation of all clinical laboratory tests taken at each visit.

Statistical analysis. Quantitative data are expressed as mean±standard deviation (SD) or median, 25th and 75th percentiles and range. Qualitative data are shown as absolute and relative frequencies. Two-group comparisons were performed with the unpaired Student's *t*-test for normally distributed quantitative data and the Mann-Whitney *U*-test for nonnormally distributed quantitative data. Inter-group differences in categorical data were analysed with the Chi-square test. Mean time to response was estimated using the Kaplan-Meier method and differences between the two groups were evaluated in a univariate analysis using the log-rank test. Analyses of variance for repeated measurements (general linear model) were performed with haemoglobin level and QoL as dependent variables, and time and group as factors. Statistical significance was defined as $p<0.05$. SPSS for Windows 11.5 software (Chicago, IL, USA) was used for all analyses.

Results

Patient disposition. A total of 119 women with gynaecological malignancies, including breast carcinoma, were enrolled (intention to treat, ITT population); 60 patients were randomly assigned to receive erythropoetin β three times weekly and 59 patients to receive erythropoetin β twice a week. The patients' flow chart is depicted in Figure 1.

Demographics, clinical and baseline characteristics. Patient characteristics were equally distributed between groups (Table I). For baseline disease characteristics see Table II. In group A and B, 95% and 97%, respectively, had received surgical therapy. A total of 97% of the patients in group A and 90% in group B underwent chemotherapy. Only 25% of group A and 15% of group B patients received radiotherapy (not significantly different, n.s.)

Response and transfusion requirements. In group A, 25 patients (45%) showed a response, whereas 31 patients (56%) in group B responded to erythropoetin ($p=0.257$). The mean time to response was 52 (47-58) days in group A *versus* 42 (37-47) days in group B ($p=0.022$). Figure 2 shows the course of Hb from baseline to study end (overall $p<0.001$). No difference was found between study groups (Figure 2). The median cumulative dose of erythropoetin β was 240,000 IU in group A and 320,000 IU in group B ($p<0.001$). Overall, 16 patients received at least one RBC transfusion: seven

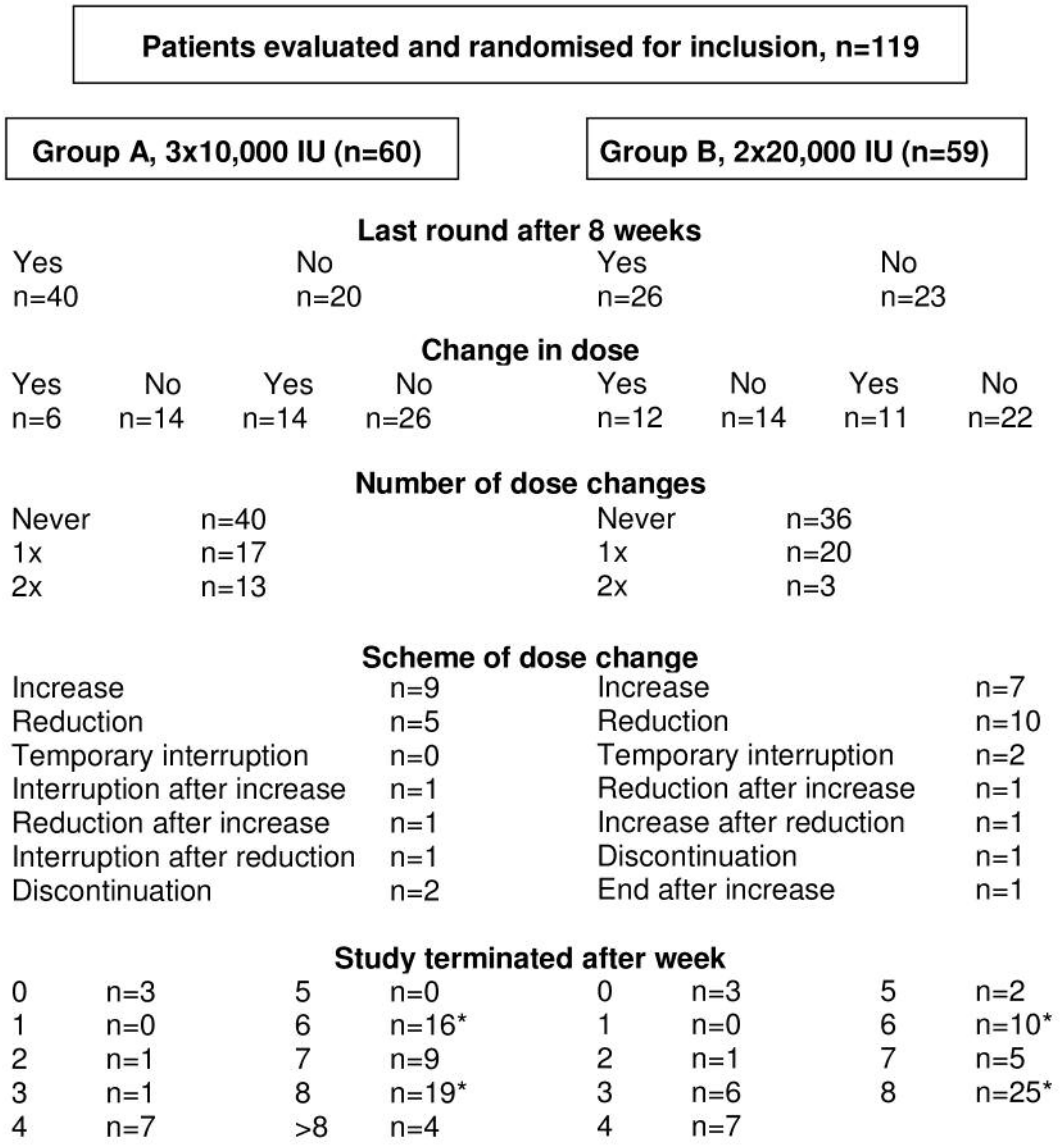

Figure 1. *Patient flow chart [intent to treat (ITT) population, n=119]. *Higher counts at 6 and 8 weeks are likely related to treatment cycles.*

(12%) patients in group A received one transfusion; in group B five (9%) patients received one, three (5%) patients two and one (1.6%) patient three transfusions (n.s.).

Quality of life. The FACT-AN module showed a significant time effect overall and for the sub-scale "Fatigue" ($p<0.05$), but there was no significant difference between study groups (mean value 51.2 to 55.2 for group A and 55.1 to 57.3 for group B).

A significant improvement in the FACT-G subscale "physical well-being" (18.2 to 20.7 in group A and 20.9 to 21.5 in group B, $p<0.05$ for both groups) was seen, whereas none of the groups was superior to the other.

Adverse events. Table III shows the observed adverse events of patients in the study groups. There were no on-study deaths. However, one patient in group B with breast carcinoma died two weeks after surgery for metastatic bone disease. In group A, three patients (5%) left the trial prematurely because of an adverse event, one patient for bone pain, one for paraesthesia and one patient was suspected of having tumour infiltration of the bone marrow. Of the seven (10%) patients in group B who discontinued the study because of an adverse event, one patient died as described above, four patients experienced thrombosis, one patient was hospitalised because of infarction of the median cerebral artery and one patient experienced febrile

Table I. *Patient demographics and baseline characteristics (ITT population, n=119).*

Characteristic [median (range)]	Group A (3×10,000 IU) n=60	Group B (2×20,000 IU) n=59	*P*-value
Age (years)	54 (30-79)	62 (28-86)	0.100
Body mass index	24.2 (16.0-36.9)	24.1 (17.2-48.1)	0.760
ECOG PS* [n (%)]			
0	16 (30%)	13 (23%)	
1	28 (52%)	38 (68%)	
2	10 (19%)	5 (9%)	0.178
Hb (g/dl, baseline)	10.3 (6.8-11.5)	10.5 (7.2-11.4)	0.541
Haematocrit (%)	31.4 (24.0-41.0)	31.0 (22.0-37.0)	0.559
Red blood cells (10^6/l)	3.5 (2.5-5.8)	3.4 (2.0-4.5)	0.101
Platelets (10^3/l)	242 (65-523)	274 (27-706)	0.399
Reticulocytes (‰)	16.4 (1.0-83.8)	17.8 (1.0-51.0)	0.535
Ferritin (μg/l)	146 (7-664)	189 (5.4-1468)	0.172

*Number of patients does not equal ITT population because of missing values. ITT, intent to treat; SD, standard deviation; ECOG PS, Eastern Cooperative Oncology Group performance status; Hb, haemoglobin.

Table II. *Baseline disease characteristics and therapy (ITT population, n=119).*

	Erythropoetin β	
	3×10,000 IU (n=60)	2×20,000 IU (n=59)
Characteristic	No. of patients (%)	No. of patients (%)
Tumour type		
Breast carcinoma	18 (30)	10 (17)
Ovarian carcinoma	30 (50)	30 (51)
Cervical carcinoma	4 (7)	5 (8)
Endometrial carcinoma	5 (8)	7 (12)
Other+	3 (5)	7 (12)
Primary tumour	24 (40)	28 (49)
Relapse	36 (60)	29 (51)
Clinical evaluation*		
No evidence of disease	11 (19)	8 (14)
Remission	7 (12)	7 (12)
Stabilisation	9 (16)	10 (17)
Progressive disease	30 (53)	33 (57)
Tumour grade*		
1	5 (19)	8 (27)
2	2 (7)	6 (20)
3	20 (74)	16 (53)
FIGO stage*		
1	8 (4)	3 (5)
2	17 (33)	15 (27)
3	32 (63)	16 (62)
4	0	1 (2)

ITT, intent to treat; FIGO, International Federation of Gynecology and Obstetrics. +Other tumours include carcinosarcoma of the uterus (n=1), carcinoma of the vulva (n=2), carcinoma of the fallopian tube (n=4), primary peritoneal cancer (n=2), borderline carcinoma of the ovary with invasive implants (n=1). *Number of patients does not equal ITT population because of missing values.

leukopenia and thrombopenia and failed to respond to erythropoetin therapy. Overall, there were eight cases of thrombosis in group B *versus* none in group A (p=0.003). The sites of thrombosis are shown in Table IV. The dose of erythropoetin was increased in three of the patients with thrombosis and reduced in one patient. Of the patients with thrombosis, three had ovarian carcinoma, two breast carcinoma, two endometrial carcinoma and one patient had primary peritoneal carcinoma. None of the patients with thrombosis had progressive disease during erythropoetin therapy; one patient had disease progression at the beginning of therapy.

In four patients Hb values increased, namely from 10.1 to 11.5 g/dl within 20 days (premature end of study due to adverse event), from 9.6 to 12.5 g/dl within 15 days (dose reduced one day before diagnosis of thrombosis, patient withdrew from the trial due to adverse event), from 11.2 to 12.8 g/dl within 20 days (study terminated because of response on the day of adverse event diagnosis) and from 9.4 to 12.5 g/dl within 20 days (premature end of study due to adverse event). In two patients with thrombosis, Hb values remained stable, namely at 10.7 g/dl and 10.9 g/dl (premature end of study in both due to adverse event). In two patients, Hb values decreased before thrombosis was diagnosed, namely from 11.2 to 9.2 g/dl within 29 days (adverse event at study end, no dose increase) and from 10.2 to 8.5 g/dl within 34 days (dose increase because of lack of response, adverse event at study end). There was no association between baseline Hb level, target Hb, Hb increase or dose change and incidence of thrombotic events in this study. For all other adverse events, no significant difference was noticed between groups.

Discussion

Anaemia is associated with reduced health-related QoL, poor treatment outcome and reduced survival (6-8). Therapy with erythropoetin has been consistently demonstrated to be effective in treating anaemia and reducing the need for RBC transfusion, and to have a positive effect on cancer-related fatigue syndrome and QoL (10, 14-18). Various regimens of erythropoetin administration have been described as being

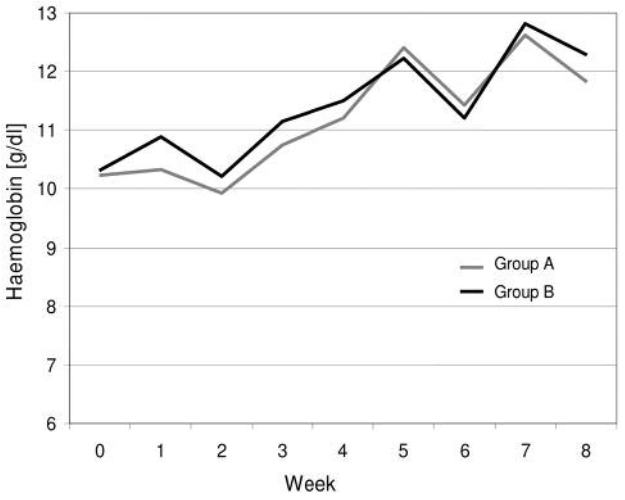

Figure 2. *Haemoglobin course from baseline to study end (week 8); (p<0.001 for response); Group A (3×10,000 IU), median 10.3 g/dl (baseline) –11.9 g/dl (study end); Group B (2×20,000 IU), median 10.5 g/dl (baseline) –12.2 g/dl (study end).*

Table III. *Observed adverse events.*

	Erythropoetin β	
	3×10,000 IU	2×20,000 IU
Adverse event	No. of cases	No. of cases
Neutropenia grade		
1-2	9	1
3-4	7	7
Febrile neutropenia	2	3
Anaemia grade 3	1	0
Thrombopenia	1	3
Pain	4	3
Dizziness	3	0
Peripheral neuropathy	2	2
Urinary infection	2	1
Erysipelas	1	2
Other infection	4	2
Nausea	2	1
Hypertension	1	1
Death	0	1
Thrombosis/embolism	0	9*

*One patient experienced a deep venous thrombosis and a pulmonary embolism.

Table IV. *Site of thrombosis.*

Site of thrombosis	Frequency
Deep venous	5
Pulmonary embolism	3
A. cerebri media infarction	1
Total	9*

*One patient experienced a deep venous thrombosis and a pulmonary embolism.

as effective as and more convenient for the patient than the standard regimen with 10,000 IU recombinant human erythropoetin administered three times weekly (19-22). A primary objective of this study was to determine whether administration of 20,000 IU of erythropoetin β twice weekly is as efficient as the standard regimen of 3×10,000 IU of erythropoetin β. Due to the fact that patients with mild anaemia (Hb<11.5 g/dl) were enrolled into the study, median Hb value at baseline was 10.3 g/dl in group A and 10.5 g/dl in group B. The median increase in Hb from baseline was 1.6 g/dl *versus* 1.7 g/dl ($p<0.001$) with no difference between the two study groups. Using a response definition of 2 mg/dl, only 45% *versus* 56% of patients responded (group A *vs.* group B, respectively; n.s.), which is less than reported in other studies (18, 20, 23). This might be due to the much shorter duration of therapy, six to eight weeks, at which the full erythropoetic response might not yet have occurred.

We observed a significant improvement in the Overall FACT-AN Score, for the FACT-AN Anemia subscale and the FACT-G subscale physical well-being but not in the other subscales. Other authors reported similar results (14, 22, 24, 25). Littlewood *et al.* (10) reported a significant improvement in all dimensions (FACT G/AN and CLAS) in the erythropoetin group as compared to the placebo group. A subsequent placebo-controlled study, however, indicated a more modest QoL benefit. Witzig *et al.* (18) found no significant improvement in QoL between patients treated with erythropoetin and placebo. However, patients who responded to erythropoetin therapy experienced a significant improvement in the FACT-AN fatigue subscale.

By the time the present trial was initiated, erythropoetin was beginning to be widely used in oncological practice. The standard dosing schedule was 10,000 IU erythropoetin administered three times weekly. In the context of recently published data (11, 12), this study again takes a critical view of the use of erythropoetin in light of the rate of thrombosis observed during this trial. The aim of the Breast Cancer Erythropoetin Survival Trial (BEST) conducted by Leyland-Jones *et al.* (11) was to determine the effect erythropoetin had on survival by maintaining a normal haemoglobin level with recombinant erythropoetin in metastatic breast cancer patients receiving first-line chemotherapy. The trial was terminated prematurely because of early increase in mortality in the erythropoetin-treated patients due to disease progression or thrombosis during the first 12 months. Most of the excess deaths in the BEST trial seemed to be the result of early

disease progression, although there was also an imbalance in deaths as a result of chemotherapy toxicity and thromboembolic events (14 suspected clots in the erythropoetin arm *versus* four in the placebo arm). Imbalances in treatment populations were discussed as one reason for this surprising result. A retrospective study by Wun *et al.* (13) compared patients without erythropoetin therapy with patients receiving either 3×10,000 IU or 2×20,000 IU recombinant human erythropoetin and found a significant difference in the incidence of symptomatic venous thrombosis (17 *versus* 2 for patients without erythropoetin, p=0.003).

In our study, there were significant clinically relevant differences in the safety profiles observed between the two dosing regimens used: in eight patients in group B (14%), a thromboembolic event was observed, whereas no thromboembolic event was recorded in group A (0%, p=0.003). The reason for this finding could not be determined sufficiently and might be a chance finding caused by the small sample size of the study, which was not powered to detect significant differences in adverse events. Both groups seemed well-balanced in age, body mass index, tumour stage and blood cell count, and no significant difference was seen between the patients with or without thrombosis with respect to thrombocytes, tumour type and primary tumour or relapse. The increase in haematocrit in all patients who experienced a thromboembolic event was not significant (32.1-35.0%). Patients known to be at high risk for thromboembolic events, *i.e.* those with a history of a thromboembolic event or thrombocythaemia, were not included in our study. Since laboratory tests for thrombophilic predisposition were not performed routinely because the number of thromboses was not a predefined endpoint of this study, underlying thrombophilic risk factors may have been distributed unevenly among the consecutively treated patients. An increase in the red blood cell mass is associated with increasing whole blood viscosity. However, our study did not demonstrate an association between mean or peak Hb and risk for thrombosis. A systematic review performed by Shehata *et al.* (26) also did not find an association between the rate of thrombembolic events and an increased concentration of hemoglobin. Neither baseline Hb level, target Hb, Hb increase nor dose change was seen to be associated with the incidence of thrombotic events in this study.

The association between cancer and an increase in the risk for thrombosis is well documented and thought to be related to advancing age, surgery, decreased activity, use of venous catheters and therapies such as tamoxifen and chemotherapy (27). There was no difference in these factors between our study groups. Cancer alone was associated with a 4.1-fold risk for thrombosis, whereas chemotherapy increased the risk to 6.5-fold (28). Overall, in 119 patients (ITT population), we observed a thromboembolic event in 6.7%, which is within the range reported in the literature (29). Bohlius *et al.* (29) recently performed a systematic meta-analysis based on 6,769 participants in 35 trials. The group observed a higher risk for a thromboembolic event in the erythropoetin group than in the placebo group (4.5% *versus* 1.4%, p<0.001). Overall, the data evaluated in that review did not show statistically significant differences in relative risks for a thromboembolic event among various subgroups as defined by pre-specified variables.

Recent results were published with the BRAVE (Breast cancer – Anaemia and the Value of Erythropoetin) trial conducted by Aapro *et al.* (30). The investigators observed thromboembolic events in 13% of the 231 patients receiving 30,000 IU epoetin β once a week *versus* 6% in the control group not receiving epoetin β therapy (n=232). The percentage of patients who experienced a serious thromboembolic event was comparable between the two study arms: 3% in the control group *versus* 4% in the epoetin β group. Another study published by Aapro *et al.* (31) describes a slightly higher frequency of thromboembolic events (5.9%) *versus* controls (4.2%) but thromboembolic-related mortality was identical in both groups (1.1%). Very recent results published by Smith *et al.* (32) also indicate an increased risk of cardiovascular and thromboembolic events in patients with active cancer not receiving chemotherapy as did the review of Bennett *et al.* (33) in which a 1.57-fold increased risk for venous thrombembolism in cancer patients receiving erythropoetin is described.

In evaluating the risks and benefits of erythropoetic agents, dose and schedule of recombinant erythropoetin therapy could matter, as might the course of the Hb level and the rate of Hb increase during treatment, even though we did not observe this. The results of our study show that both treatment schedules used in this protocol result in a significant and similar increase in Hb and QoL. The overall rate of thromboembolic events in this study (6.7%) is within the known adverse event profile of erythropoetic agents in cancer patients. Although there was a significant difference in thrombotic events between the two study groups (8 *versus* 0, p=0.003), we could not find any clinical parameters or routine laboratory tests to identify those patients who developed thrombosis. In fact, Hb response was similar in the two study arms.

In conclusion, our study did not not show any difference in Hb increase or other investigated markers of efficacy of epoetin therapy such as response rates, transfusions or QoL between the two dosing regimens. However, a significantly higher rate of thromboembolic events was observed in the higher-dosed group than in the lower- (standard)-dosed group. We were not able to explain this difference by imbalances in risk factors in the two groups, nor did we find any potential association with Hb or haematocrit increase and occurrence of the thromboembolic events.

Conlusion

We do, however, believe that these findings warrant particular attention with respect to using higher doses of epoetin at reduced dosing frequencies in patients with gynaecological or breast cancer who are, by their disease status, at an increased risk of experiencing thromboembolic complications.

Conflict of Interest

All authors disclose they have no financial or personal relationships with other people or organisations that could inappropriately influence their work

Acknowledgements

The study was funded by the "Studienzentrale der Arbeitsgemeinschaft Gynäkologische Onkologie Austria", which is an academic study group in Austria and performs multicenter trials within the country. Erythropoetin β 20,000 IU was funded by NeoRecormon®; Hoffmann-La Roche Ltd, Basel, Switzerland.

References

1 Tas F, Eralp Y, Basaran M, Sakar B, Alici S, Argon A, Bulutlar G, Camlica H, Aydiner A and Topu E: Anemia in oncology practice: relation to diseases and their therapies. Am J Clin Oncol *25*: 371-379, 2002.

2 Knight K, Wade S and Balducci L: Prevalence and outcomes of anemia in cancer: a systematic review of the literature. Am J Med *116*: 11-26 (Suppl 7A), 2004.

3 Groopman JE and Itri LM: Chemotherapy-induced anemia in adults: incidence and treatment. J Natl Cancer Inst *91*: 1616-1634, 1999.

4 Fein DA, Lee WR, Hanlon AL, Ridge JA, Langer CJ, Curran WJ Jr and Coia LR: Pretreatment hemoglobin level influences local control and survival of T1-T2 squamous cell carcinomas of the glottic larynx. J Clin Oncol *13*: 2077-2083, 1995.

5 Bush RS, Jenkin RD, Allt WE, Beale FA, Bean H, Dembo AJ and Pringle JF: Definitive evidence for hypoxic cells influencing cure in cancer therapy. Br J Cancer *37(3)*: 302-306, 1978.

6 Caro JJ, Salas M, Ward A and Goss J: Anemia as an independent prognostic factor for survival in patients with cancer: a systemic, quantitative review. Cancer *91(12)*: 2214-2221, 2001.

7 Straus DJ, Gaynor JJ, Myers J, Merke DP, Caravelli J, Chapman D, Yahalom J and Clarkson BD: Prognostic factors among 185 adults with newly diagnosed advanced Hodgkin's disease treated with alternating potentially noncross-resistant chemotherapy and intermediate-dose radiation therapy. J Clin Oncol *8(7)*: 1173-1186, 1990.

8 Grogan M, Thomas GM, Melamed I, Wong FL, Pearcey RG, Joseph PK, Portelance L, Crook J and Jones KD: The importance of hemoglobin levels during radiotherapy for carcinoma of the cervix. Cancer *86(8)*: 1528-1536, 1999.

9 Cella D, Kallich J, McDermott A and Xu X: The longitudinal relationship of hemoglobin, fatigue and quality of life in anemic cancer patients: results from five randomized clinical trials. Ann Oncol *15(6)*: 979-986, 2004.

10 Littlewood TJ, Bajetta J, Vercammen E, Nortier JW and Rapoport B: Effects of epoetin alfa on hematologic parameters and quality of life in cancer patients receiving nonplatinum chemotherapy: results of a randomized, double-blind, placebo-controlled trial. J Clin Oncol *19(11)*: 2865-2874, 2001.

11 Leyland-Jones B, Semiglazov V, Pawlicki M, Pienkowski T, Tjulandin S, Manikhas G, Makhson A, Roth A, Dodwell D, Baselga J, Biakhov M, Valuckas K, Voznyi E, Liu X and Vercammen E: Maintaining normal hemoglobin levels with epoetin alfa in mainly nonanemic patients with metastatic breast cancer receiving first-line chemotherapy: a survival study. J Clin Oncol *23(25)*: 5960-5972, 2005.

12 Henke M, Laszig R, Rübe C, Schafer U, Haase KD, Schilcher B, Mose S, Beer KT, Burger U, Dougherty C and Frommhold H: Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: randomised, double-blind, placebo-controlled trial. Lancet *362*: 1255-1260, 2003.

13 Wun T, Law L, Harvey D, Sieracki B, Scudder SA and Ryu JK: Increased incidence of symptomatic venous thrombosis in patients with cervical carcinoma treated with concurrent chemotherapy, radiation and erythropoietin. Cancer *98*: 1514-1520, 2003.

14 Chang J, Couture F, Young S, Mc Watters KL and Lau CY: Weekly epoetin alfa maintains hemoglobin, improves quality of life and reduces transfusion in breast cancer patients receiving chemotherapy. J Clin Oncol *23(12)*: 2597-2605, 2005.

15 Ludwig H, van Belle S, Barrett-Lee P, Birgegard G, Bokemeyer C, Gascon P, Kosmidis P, Krzakowski M, Nortier J, Olmi P, Schneider M and Schrijvers D: The European Cancer Anaemia Survey (ECAS): A large, multinational, prospective survey defining the prevalence, incidence, and treatment of anaemia in cancer patients. Eur J Cancer *40*: 2293-2306, 2004.

16 Boogaerts M, Coiffier B and Kainz C: Impact of epoetin β on quality of life in patients with malignant disease. Br J Cancer *88*: 988-995, 2003.

17 Demetri GD, Kris M, Wade J, Degos L and Cella D: Quality of life benefit in chemotherapy patients treated with epoetin alfa is independent of disease response or tumor type: results from a prospective community oncology study. Procrit Study Group. J Clin Oncol *16*: 3412-3425, 1998.

18 Witzig TE, Silberstein PT, Loprinzi CL, Sloan JA, Novotny PJ, Mailliard JA, Rowland KM, Alberts SR, Krook JE, Levitt R and Morton RF: Phase III, randomized, double-blind study of epoetin alfa compared with placebo in anemic patients receiving chemotherapy. J Clin Oncol *23*: 2606-2617, 2005.

19 Gabrilove JL, Cleeland CS, Livingston RB, Sarokhan B, Winer E and Einhorn LH: Clinical evaluation of once-weekly dosing of epoetin alfa in chemotherapy patients: Improvements in hemoglobin and quality of life are similar to three-times-weekly dosing. J Clin Oncol *19*: 2875-2882, 2001.

20 Cazzola M, Beguin Y, Kloczko J, Spicka I and Coiffier B: Once-weekly epoetin beta is highly effective in treating anaemic patients with lymphoproliferative malignancy and defective endogenous erythropoetin production. B J Haematology *122*: 386-393, 2003.

21 Pujade-Lauraine E, Richard AJ, Sapede C and Hayward C: Erythropoietic agents in anaemic patients with cancer: a retrospective observational survey of epoetin alpha, epoetin beta and darbepoetin alpha use in routine clinical practice. Oncol Rep *14(4)*: 1037-1044, 2005.

22 Waltzman R, Croot C, Justice GR, Fesen MR, Charu V and Williams D: Randomized comparison of epoetin alfa (40,000 IU weekly) and darbepoetin alfa (200 μg every 2 weeks) in anemic patients with cancer receiving chemotherapy. Oncologist *10*: 642-650, 2005.

23 Vansteenkiste J, Pirker R, Massuti B, Barata F, Font A, Fiegl M, Siena S, Gateley J, Tomita D, Colowick AB and Musil J: Double-blind, placebo-conrolled, randomized phase III trial of darbepoetin alfa in lung cancer patients receiving chemotherapy. J Natl Cancer Inst *94*: 1211-1220, 2002.

24 Glaspy J, Degos L, Dicato M and Demetri GD: Comparable efficacy of epoetin alfa for anemic cancer patientis receiving platinum- and nonplatinum-based chemotherapy: a retrospective subanalysis of two large, community-based trials. Oncologist *7*: 126-135, 2002.

25 Reinhardt U, Tulusan A, Angermund R and Lutz H: Increased hemoglobin levels and improved quality-of-life assessments during epoetin alfa treatment in anemic cancer patients: results of a prospective, multicenter German trial. Oncologist *10*: 225-237, 2005.

26 Shehata N, Walker I, Meyer R, Haynes AE, Imrie K for the Cancer Care Ontario Hematology Disease Site Group: The use of erythropoiesis-stimulating agents in patients with non-myeloid haematological malignancies: a systematic review. Ann Haematol: 16, 2008.

27 Lee AY and Levine MN: Venous thromboembolism and cancer: risks and outcomes. Circulation *107*: 117-121 (review), 2003.

28 Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM and Melton LH 3rd: Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. Arch Intern Med *160*: 809-815, 2000.

29 Bohlius J, Wilson J, Seidenfeld J, Piper M, Schwarzer G, Sandercock J, Trelle S, Weingart O, Bayliss S, Djulbegovic B, Bennett CL, Langensiepen S, Hyde C and Engert A: Recombinant human erythropoietins and cancer patients: updated meta-analysis of 57 studies including 9353 patients. J Nat Cancer Inst *98*: 708-714 (review), 2006.

30 Aapro M, Leonard RC, Barnadas A, Marangolo M, Untch M, Malamos N, MayordomoJ, Reichert T, Pedrini JL, Ukarma L, Scherhag A and Burger H: Effects of once-weekly epoetin beta on survival in patients with metastatic breast cancer receiving anthracycline- and/or taxane-based chemotherapy. Results of the Breast Cancer-Anemia and the Value of Erythropoietin (BRAVE) Study. J Clin Oncol *26(4)*: 592-598, 2008 .

31 Aapro M, Coiffier B, Dunst J, Österborg A and HU Burger: Effect of treatment with epoetin beta on short-term tumour progression and survival in anaemic patients with cancer: a meta-analysis. Br Cancer *95*: 1467-1473, 2006.

32 Smith R, Aapro M, Ludwig H, Pintèr T, Smakal M, Ciuleanu T, Chen L, Lillie T and Glaspy J: Darbepoetin alfa for the treatment of anemia in patients with active cancer not receiving chemotherapy or radiotherapy: results of a phase III, multicenter, randomized, double-blind, placebo-controlled study. J Clin Oncol *26(7)*: 1040-1050, 2008.

33 Bennett C, Silver S, Djulbegovic B, Samaras A, Blau A, Gleason K, Barnato S, Elverman K, Courtney D, McKay J, Edwards B, Tigue C, Raisch D, Yarnold P, Dorr D, Kuzel T, Tallman M, Trifilio S, Wet D, Lai S and Henke M: Venous thromboembolism and mortality associated with recombinant erythropoietin and darbepoetin administration for the treatment of cancer-associated anemia. J Am Med Assoc *299(8)*: 914-924, 2008.

Received May 21, 2008
Revised August 22, 2008
Accepted September 30, 2008