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Critical Reviews in Oncology/Hematology 69 (2009) 175–182

CRITICAL REVIEWS IN
Oncology
Hematology
Incorporating Geriatric Oncology

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Effect of age on hemoglobin levels and quality of life following treatment with epoetin alfa in cancer patients

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Accepted 11 July 2008

Contents

Abstract

A subgroup analysis comparing elderly (age ≥70 years; $n = 95$) with younger (age <70 years; $n = 390$) patients was performed on data from a prospective, multicenter, open-label study assessing the effects of once-weekly epoetin alfa 40,000 International Units (IU) for 16–20 weeks on hemoglobin (Hb) levels and quality of life (QoL) in anemic adult patients undergoing chemotherapy for solid tumors. There were significant increases in mean Hb levels at 4, 8, 12, 16–20 weeks in both age groups ($p < 0.0001$), but no significant differences between groups ($p = 0.7$). No significant difference was observed in terms of blood transfusion rates across the study between elderly and younger patients (3.2% vs

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1040-8428/$ – see front matter
doi:10.1016/j.critrevonc.2008.07.010

6.7%, $p = 0.2$). Although QoL was lower in elderly patients at baseline, the relative percentage increases in QoL scores during treatment were similar for both age groups. Thus, once-weekly epoetin alfa was equally effective in treating chemotherapy-related anemia in elderly and younger adult patients, with similar tolerability.

Keywords: Anemia; Elderly patients; Epoetin alfa; Quality of life; Solid tumors

1. Introduction

Anemia is common in cancer patients, resulting from either the disease itself or aggressive chemotherapy/radiotherapy, and produces fatigue as its cardinal consequence, but also produces other symptoms such as headache, dizziness, dyspnea, chest pain, weakness, depression, palpitations and decreased cognitive function [1–3]. These symptoms contribute significantly to the decrease in the quality of life (QoL) of cancer patients [1].

A number of clinical trials have demonstrated that the treatment of cancer-related anemia with epoetin alfa (recombinant human erythropoietin), administered either three times weekly or once weekly, significantly increases hemoglobin (Hb) levels, reduces transfusion requirements, and improves patients' QoL, in large part by relieving fatigue [4–8]. The improvements in QoL positively correlated with the increases in Hb level and were independent of tumor response to chemotherapy [4,5].

Although estimates vary widely and have been contradictory, anemia is generally considered to have a higher prevalence in the elderly, usually with a sharp rise after the age of 70 years [9]. In the elderly population, the impact of anemia may lead to limitations in mobility, increased falls, depression and increased cardiovascular risk; all events that contribute to the development of frailty [9,10].

We recently reported the results of a prospective, uncontrolled, open-label trial of epoetin alfa 40,000 International Units (IU) administered once weekly for up to 20 weeks in 522 patients with anemia secondary to chemotherapy for solid tumors [11]. The results of this study demonstrated that correction of anemia with epoetin alfa was associated with improvement in patients' QoL.

Since no other studies reported on the effect of epoetin alfa treatment in a large population of elderly patients, the purpose of this analysis was to assess potential differences in increases of Hb levels and QoL scores between younger and elderly patients during epoetin alfa treatment.

2. Patients and methods

A subgroup analysis was performed in elderly patients, aged 70 years and older, in comparison with younger patients, aged less than 70 years, participating in a previously reported, prospective, uncontrolled, open-label trial conducted across 61 clinical centres in Italy [11]. Local Ethics Review Boards approved the protocol and all patients gave their written informed consent before study enrollment. The study was conducted according to the Declaration of Helsinki.

2.1. Patient selection

Criteria for entry into the original trial were: age ≥18 years; histologically confirmed solid malignancy (breast, lung, gynecological, or gastrointestinal tumor); Hb level ≤12 g/dL; an Eastern Cooperative Oncology Group (ECOG) performance score ≤2; a life expectancy ≥6 months; and scheduled to receive chemotherapy for at least 9 weeks. The main exclusion criteria were: serious concomitant conditions unrelated to the malignant disease; anemia unrelated to the malignant disease or its treatment; untreated iron, folate, or vitamin B_{12} deficiency; uncontrolled hypertension (diastolic blood pressure >95 mm Hg); thromboembolic or vascular accidents in the previous 6 months; blood transfusion in the previous 14 days; symptomatic or untreated brain metastases; clinically relevant infectious disease or surgery in the previous 7 days; and treatment with epoetin in the previous 4 weeks.

2.2. Treatment administration

Epoetin alfa (Eprex®, Ortho Biotech, a division of Janssen-Cilag SpA) was provided as 1 mL vials containing 40,000 IU and was administered by subcutaneous injection. The recommended treatment outline is shown in Fig. 1. All patients were initially treated with epoetin alfa 40,000 IU once weekly for 4–6 weeks in order to reach and maintain an Hb level of 13–14 g/dL. A dosage increase to 60,000 IU once weekly after the initial 4–6 weeks was recommended if the Hb level was <10.5 g/dL, Hb increased <1 g/dL from baseline, and reticulocyte count increased by <40,000/μL from baseline. Therapy was continued for a maximum duration of 20 weeks. Dosage reduction by 25% (e.g. from 40,000 to 30,000 IU) was recommended if the Hb level increased too rapidly (by ≥2 g/dL in 1 month or ≥1.5 g/dL in 3 weeks). Whenever the Hb level exceeded 14 g/dL, epoetin alfa treatment was suspended until the Hb level fell below 12 g/dL and was then restarted with the dose reduced by 25%.

Blood transfusions were permitted for Hb level <9 g/dL or symptoms of anemia. Supplementation with 200 mg elemental iron (oral) daily was recommended whenever transferrin saturation was ≤20%. Concomitant treatment with leukocyte growth factors was permitted.

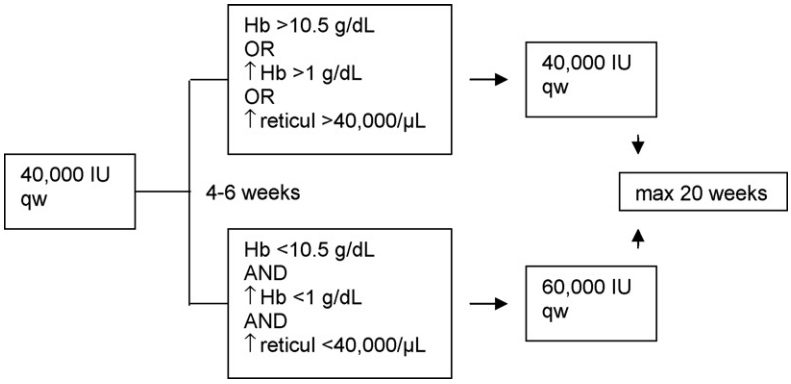

Fig. 1. Recommended study treatment outline. Hb: hemoglobin; IU: international units; max: maximum; qw: once weekly; reticul: reticulocytes; (↑) denotes increase in value.

2.3. Assessments

Hb levels were monitored at least every 4 weeks throughout the study. QoL was assessed using the Functional Assessment of Cancer Therapy-Anemia subscale (FACT-An), a self-administered questionnaire composed of 20 items, and the Cancer Linear Analogue Scale (CLAS) consisting of three 100 mm visual analog scales measuring energy levels, ability to perform daily life activities, and overall QoL [12]. Possible scores range from 0 to 80 for FACT-An and 0 to 100 for CLAS, with higher scores in each scale representing better QoL. FACT-An and CLAS were administered at baseline, after two cycles of chemotherapy (usually 6–8 weeks), and at study end. Patients were not aware of their Hb level at the time of completing the QoL assessments.

Blood transfusion requirements and adverse events were recorded throughout the study.

2.4. Statistical analysis

Statistical analyses were performed with data from all patients who did not incur major violations of selection criteria, had at least one dose of study drug, and had at least one post-enrollment visit. Hb values and QoL measures were reported using means and standard deviations.

Summary of Hb statistics was calculated at baseline, after 4, 8 and 12 weeks (allowing for ±2 weeks around interval midpoint due to different lengths of chemotherapy cycles), and for the last on-study measure in the interval from day 99 to 154. Other summary measures of erythropoietic response were the proportions of patients who had achieved an Hb increase ≥1 or ≥2 g/dL during the study; this parameter has been calculated by means of crude rate, Kaplan–Meier estimates, log-rank test, and Cox regression models. The rate of transfusion during the study was also calculated.

Manova test was used to test the difference in Hb variations over time and according to the age group. Linear regression models were used to test the relationship among Hb increases from the baseline to week 8 and study end and the following variables: age, sex, stage of disease, performance status, Hb at baseline, and previous transfusions.

FACT scores were coded and summed according to the Functional Assessment of Chronic Illness Therapy (FACIT) manual, and the three CLAS scores were averaged to obtain a single CLAS mean score. Summary FACT-An and CLAS statistics were calculated at baseline, at an intermediate evaluation scheduled after two chemotherapy cycles (usually 6–8 weeks, actual range 15–70 days), and at end of study. Manova test was used to test the difference in FACT-An variations over time and according to the age group. The same test was carried out for CLAS scores. Pearson's correlation coefficient was calculated between QoL scores (FACT-An and CLAS) and Hb level at baseline, week 8 and study end. The relationship between QoL scores and Hb increases from the baseline to intermediate and final evaluations were also investigated using linear regression models. Multivariate regression analysis was used to test the relation among QoL scores and the following variables: age, sex, stage of disease, performance status, Hb at baseline, Hb levels, and previous transfusions.

Safety was assessed by recording adverse events. Incidence rates overall and by type of adverse event (coded according to the WHO-ART system) were calculated for all patients who had taken at least one dose of the study drug. Data analyses were performed using the Statistical Analysis System (SAS®, SAS Institute, Cary, NC), release 8.2 and 9.1.

3. Results

Of the 485 evaluable patients comprising the efficacy population in the original trial, 95 were aged ≥70 years. Baseline demographics and clinical characteristics of the patient population are detailed in Table 1. Elderly patients were generally affected by more advanced disease, with a higher prevalence of gastrointestinal and lung cancer and a worse performance status than the younger subpopulation. No statistically significant difference was observed according to the age group in terms of concomitant chemotherapy with platinum-based regimens (chi square, $p = 0.3$).

Table 1
Baseline demographics and clinical characteristics of the study population assessed for efficacy.

	Overall	<70 years	≥70 years
Sex, *n* (%)	(*N* = 485)	(*N* = 390)	(*N* = 95)
Male	160 (33.0)	110 (28.2)	50 (52.6)
Female	325 (67.0)	280 (71.8)	45 (47.4)
Age (years)	(*N* = 485)	(*N* = 390)	(*N* = 95)
Mean ± S.D.	60.11 ± 11.03	56.71 ± 9.44	74.04 ± 3.61
Weight (kg)	(*N* = 482)	(*N* = 387)	(*N* = 95)
Mean ± S.D.	65.53 ± 12.3	65.45 ± 12.57	65.87 ± 11.23
Primary tumor type, *n* (%)	(*N* = 485)	(*N* = 390)	(*N* = 95)
Lung	82 (16.9)	60 (15.48)	22 (23.2)
Breast	142 (29.3)	129 (33.1)	13 (13.7)
Gynecological	71 (14.6)	60 (15.4)	11 (11.6)
Gastrointestinal	183 (37.7)	135 (34.6)	48 (50.5)
Stage of tumor, *n* (%)	(*N* = 485)	(*N* = 390)	(*N* = 95)
Early	119 (24.5)	103 (26.4)	16 (16.8)
Locally advanced	94 (19.34)	70 (18.0)	24 (25.3)
Metastatic	269 (55.5)	215 (55.1)	54 (56.8)
Not reported	3 (0.6)	2 (0.5)	1 (1.1)
Hemoglobin (g/dL), *n* (%)	(*N* = 484)	(*N* = 389)	(*N* = 95)
Mean	10.43 ± 0.98	10.44 ± 0.99	10.40 ± 0.98
<9	47 (9.7)	39 (10.0)	8 (8.4)
9–10	108 (2.3)	83 (21.3)	25 (26.3)
>10	329 (68.0)	267 (68.6)	62 (65.3)
ECOG performance status, *n* (%)	(*N* = 485)	(*N* = 390)	(*N* = 95)
0	285 (58.8)	238 (61.0)	47 (49.5)
1	163 (33.6)	124 (31.8)	39 (41.1)
2	36 (7.4)	27 (6.9)	9 (9.5)
Not reported	1 (0.2)	1 (0.3)	0 (0)
Concomitant chemotherapy, *n* (%)	(*N* = 485)	(*N* = 390)	(*N* = 95)
Platinum-based	212 (43.7)	175 (44.9)	37 (39.0)
Without platinum	273 (56.0)	215 (55.1)	58 (61.0)
Concomitant radiotherapy, *n* (%)	(*N* = 485)	(*N* = 390)	(*N* = 95)
	16 (3.3)	11 (2.8)	5 (5.3)

3.1. Hemoglobin values

Hb values in both the elderly and younger subpopulations increased from mean baseline levels of 10.40 and 10.44 g/dL, respectively, to attain levels ≥12 g/dL after 8 weeks of therapy (Fig. 2). Mean changes from baseline in Hb, which were calculated within patients rather than as means for the group, increased steadily over 12 weeks, then plateaued or decreased slightly by study end (Manova test, $p < 0.0001$) (Table 2). There were no significant differences in Hb values between elderly and younger patients (Manova test, $p = 0.7$). The incidence of blood transfusion was numerically slightly lower in the elderly than in the younger population (3.2% vs 6.7%), although the difference did not reach statistical significance (chi square, $p = 0.2$).

Multivariate analysis, at week 8, showed that patients with advanced disease ($p = 0.04$), Hb >9 g/dL at baseline ($p = 0.03$)

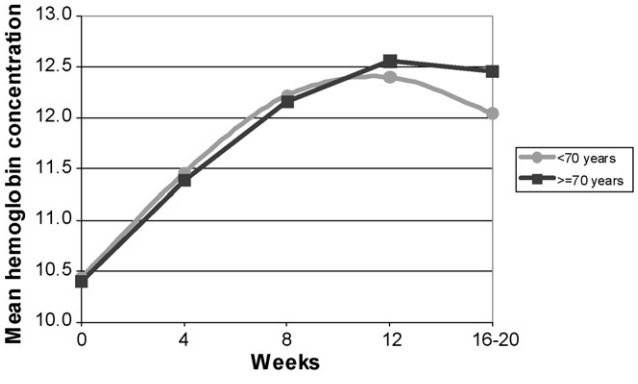

Fig. 2. Mean hemoglobin concentration (g/dL) from baseline to end of study.

Table 2
Mean change from baseline in Hb values in elderly and younger patients.

Age group	Mean change in Hb value (g/dL)[a]			
	4 weeks	8 weeks	12 weeks	Study end[b]
Elderly	1.01	1.77	2.06	2.06
Younger	1.04	1.73	1.89	1.57

[a] Changes in Hb values were calculated within patients rather than by calculating the difference for the group means.
[b] Manova test: time effect *p*-value <0.0001; age effect *p*-value 0.680.

Table 3
Linear regression analysis of Hb levels at week 8 and study end.

Parameter	Increase of Hb levels (g/dL) from baseline to week 8[a]		Increase of Hb levels (g/dL) from baseline to study end[b]	
	Parameters estimates	*p*-Value	Parameters estimates	*p*-Value
Intercept	2.68621	<0.0001	2.84701	<0.0001
Locally advanced and metastatic vs early	−0.34324	0.0432	–	–
Hb level at baseline >9 g/dL vs Hb level at baseline ≤9 g/dL	−0.57515	0.0266	−1.14836	<0.0001
Patients transfused within week 8 vs not transfused	−1.67171	<0.0001	–	–
ECOG 1–2 vs ECOG 0	–	–	−0.54384	0.0006

[a] Adjusted for sex, age, and performance status.
[b] Adjusted for sex, age, tumor stage, and transfusions.

and those receiving blood transfusions before the 8th week ($p < 0.0001$) experienced a statistically lower increase in Hb levels (Table 3). At study end only the patients with a worse ECOG PS and an Hb value >9 showed a significantly lower Hb increase.

The crude response rate of patients increasing their Hb >1 g/dL as early as week 4 is 51.6% (data not shown). The proportion of patients achieving an Hb increase ≥2 g/dL at the end of treatment in the elderly and younger populations was calculated by two different methods (Table 4). The crude rate represents the percentage of patients with an Hb increase ≥2 g/dl at the study end, while the Kaplan–Meier estimate takes into account the cumulative patients reaching the same increase at any time during the study. At a multivariate analysis all the patients experienced the same response rate except for the early stage disease vs metastatic disease (Cox regression model, data not shown).

3.2. Quality of life

The compliance rates (percentage of the patients that answered the questionnaires) for QoL data were 100%, 86% and 95%, respectively at baseline, week 8 and study end. The same rates were calculated according to the age group and were 100%, 86%, and 95% in younger patients, and 100%, 85% and 96% in older patients. No differences in compliance rates were observed according to age group at week 8 (chi square, $p = 0.8$) or at study end (chi square, $p = 0.6$).

During treatment with epoetin alfa patients' QoL scores increased in both the elderly and younger adult populations as shown in Fig. 3. Elderly patients had poorer QoL than younger patients at baseline and throughout the study as assessed by both the FACT-An and CLAS scores. QoL scores in the elderly population were maximal at the intermediate assessment point at the end of two cycles of chemotherapy (usually 6–8 weeks) (Fig. 3), when patients' Hb levels were at or approaching 12 g/dL, and were maintained thereafter at slightly reduced levels.

The increases in mean values from baseline in FACT-An scores did not differ significantly during the study (Manova test, $p = 0.7$) nor between the two age groups (Manova test, $p = 0.8$). Similar results were observed for CLAS scores (Manova test, $p = 0.3$ and 0.1, respectively, for time effect and age effect). Multivariate analysis showed a significant improvement in FACT-An scores in patients with better performance status ($p = 0.0001$) and in patients experiencing an increase in Hb levels ($p = 0.003$). Similarly, a statistically significant improvement in CLAS scores was observed in patients with better performance status ($p < 0.0001$) and in patients experiencing an increase in Hb levels ($p = 0.003$).

Table 4
Proportion of patients achieving an Hb increase of ≥2 g/dL.

Age group	Hb increase ≥2 g/dL	
	Crude rate (chi square test, $p = 0.005$) (%)	Kaplan–Meier estimate (log-rank test, $p = 0.6$) (%)
<70 years ($n = 354$)	37.9	76.2
≥70 years ($n = 86$)	54.7	76.9
Overall	41.1	76.4

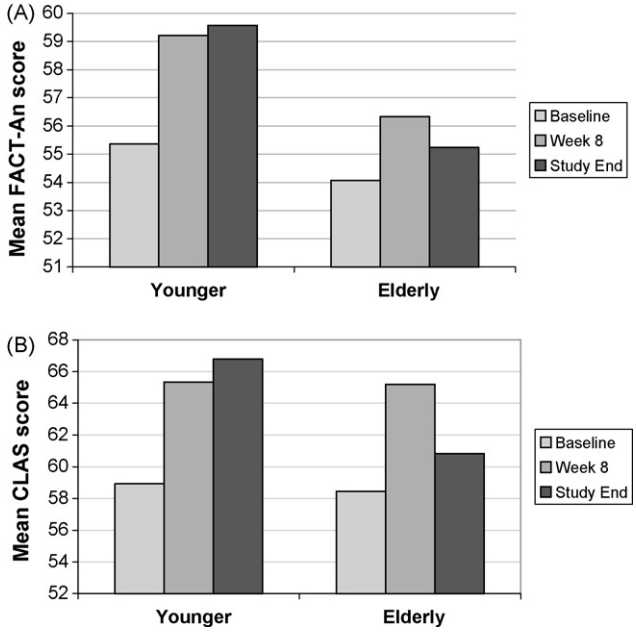

Fig. 3. Quality of life measures for elderly and younger populations over time. (A) Mean FACT-An score; (B) mean CLAS score.

3.3. Tolerability

Epoetin alfa was well tolerated, with the most commonly reported adverse events in both groups being related either to chemotherapy or the disease itself. Adverse events reported by 5% or more of patients were granulocytopenia (16.7%), nausea (7.9%), vomiting (6.3%), fever (6.3%), thrombocytopenia (5.9%), asthenia (5.4%), leukopenia (5.2%), and abdominal pain (5.0%).

Despite higher age being an expected risk factor, the incidence of thromboembolic events (deep vein thrombosis and pulmunar embolism) was not significantly different between elderly and younger patients (2.1% vs 5.4%, respectively, $p = 0.3$). Similarly, no significant difference was observed in terms of non-serious vascular events (thromboflebitis) between the two age groups (2.1% vs 1% for elderly and younger patients, respectively).

4. Discussion

Patients aged ≥70 years are highly representative of the cancer population and anemia is known to be an independent risk factor for cardiovascular disease, increased functional dependence and death in the elderly population.

Elderly patients, comprised a significant proportion (20%) of the patients from an open-label, multicenter study assessing the effects of treatment with epoetin alfa 40,000 IU once weekly on Hb levels and QoL in anemic patients undergoing chemotherapy for solid tumors [11]. This paper describes the characteristics of the age stratum ≥70 years old as per protocol and compares elderly with younger adult population under the same study conditions.

In this analysis we confirmed that erythropoietic agents are equally effective in both adult and elderly cancer population undergoing chemotherapy as previously seen in small studies [13–15] and very recently published in a large cohort study [16].

In both subpopulations, Hb levels increased by approximately 1 g/dL as early as 4 weeks after initiating the treatment with epoetin alfa and approached 12 g/dL from week 8 onwards with no significant differences between the two groups. Similarly, transfusion requirements did not differ significantly between the elderly and younger adult populations. Interestingly, different results were seen in elderly and younger populations according to the method used to calculate the hematologic response (crude rate at the end of treatment vs the cumulative response during the study) (Table 4). Differences in the outcome observed with the two analyses might be explained with drug discontinuation once the Hb target had been achieved.

Therefore some caution should be used when comparing data among different studies, not only because of different patients' characteristics but also for the possible difference in the response definition and statistical methods applied.

Our study provided some insights on potential determinants of benefit from the treatment with epoetin alfa. In particular, at week 8, multivariate analysis showed that patients with advanced disease, Hb >9 g/dL at baseline and those receiving blood transfusions before the 8th week experienced a statistically lower increase in Hb levels (Table 3). However, these results must be interpreted with caution because of the retrospective analysis and small sample size in each subgroup.

QoL was higher in the younger population than in the elderly population throughout the study, but this appeared to be simply a reflection of the lower baseline QoL in the elderly patients, resulting from a lower performance status and more advanced disease at baseline. In addition, elderly patients could be expected to have an overall lower QoL based on age alone. The actual quantitative percentage increases in QoL scores did not differ significantly between the two age groups, particularly at the interim assessment after two chemotherapy cycles, for either the FACT-An or CLAS scales.

The incidence of adverse events was similar in both age groups, even in thromboembolic events. Unexpectedly, although older age is known to be a risk factor, a non-significant lower incidence of serious thromboembolic events was observed in patients of age ≥70 years (2.1% vs 5.4%, $p = 0.3$). The incidence of thromboembolic events observed in this analysis is lower than the 7% incidence seen with three times weekly administration of epoetin alfa (150–300 IU/kg) in a previous randomized, double-blind, placebo-controlled trial [7]. In that trial however, no distinction was made between thrombotic and possible thrombotic events. In addition, studies are not easily comparable because of the differences in study populations.

On the contrary, the percentage of thromboembolic events in our study was of a similar magnitude to that reported in a recent randomized study exploring the efficacy of once-weekly epoetin beta in patients with metastatic breast cancer receiving anthracycline- and/or taxane-based chemotherapy [17].

At the time this trial was designed, issues regarding increased risk of death and cardiovascular events in patients treated with epoetin to a target Hb level higher than 12 g/dL were not as widely highlighted. Consequently, patients with Hb level ≤12 g/dL were enrolled in the trial and treated with epoetin alfa to reach and maintain an Hb value of 12–14 g/dL.

Adverse outcomes in recent trials conducted outside the indications (i.e. beyond anemia or without chemotherapy treatment) on all the marketed erythropoietic agents have generated an ongoing discussion on the recommended target Hb level (reviewed by Khuri, 2007 [18]). American and European authorities have now recommended the treatment of anemic cancer patients undergoing chemotherapy with erythropoietic agents to a target of 12 g/dL.

In summary, once-weekly epoetin alfa was equally effective in treating anemia in elderly and younger adult patients undergoing chemotherapy for solid tumors. Both age groups had similar transfusion requirements and experi-

enced similar increases in Hb levels and QoL scores. Elderly patients did not appear to be at increased risk of adverse events.

Reviewers

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Acknowledgments

Dr. Valentina Rosolen provided assistance with statistical analysis.

Editorial support for the preparation of the manuscript was provided by Wolters Kluwer Health Medical Communications.

Andrea Sporchia is partly supported by grants from Oncologia Cà Granda Onlus (OCGO) Fondazione.

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Role of the funding source: this study was sponsored by Janssen Cilag SpA Italy.

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Biography

Fabio Puglisi (M.D., Ph.D.) is a senior staff member of the Department of Medical Oncology, University Hospital of Udine, Italy. In 1993, he received his degree in medicine (cum laude) from the University of Palermo, Italy. He undertook his post-graduate training in oncology at the University Hospital of Udine, receiving its certification of specialization in oncology (cum laude) in 1997. In January 2002, Dr. Puglisi received the title of Ph.D. in diagnostic quantitative pathology from the University of Siena, Italy. In 1996, he attended the Breast Unit, City Hospital NHS Trust, Nottingham, UK (Dr. I.O. Ellis) as visiting research fellow. In 2005, he attended the Clinique d'Oncologie Médicale, Service de Médicine Interne, Institut Jules Bordet, Bruxelles, BE (Prof. M.J. Piccart) as visiting research fellow. He is the author of several publications in scientific peer-reviewed journals, especially in his main fields of interest (i.e. clinical trials on breast cancer treatment and research on prognostic and predictive factors). Since 1998, Dr. Puglisi has held his teaching activity mainly for the University of Udine, Italy and in regional and national courses. He is an active member of American Society of Clinical Oncology (ASCO), International Breast Cancer Study Group (IBCSG), Italian Association of Medical Oncology (AIOM), Gruppo Italiano Mammella (GIM). As an expert on clinical trials in oncology, he served on the Board of the Ethical Committee of the General Hospital of Trieste, Italy.