Anemia Is a Significant Prognostic Factor in Local Relapse-Free Survival of Premenopausal Primary Breast Cancer Patients Receiving Adjuvant Cyclophosphamide/Methotrexate/5-Fluorouracil Chemotherapy

Peter Dubsky,[1] Paul Sevelda,[5] Raimund Jakesz,[1] Hubert Hausmaninger,[7] Hellmut Samonigg,[8] Michael Seifert,[2] Ursula Denison,[5] Brigitte Mlineritsch,[7] Günther Steger,[3] Werner Kwasny,[9] Herbert Stöger,[8] Rupert Bartsch,[3] Michael Stierer,[6] Susanne Taucher,[1] Michael Fridrik,[10] Walter Schippinger,[8] Richard Greil,[7] Richard Pötter,[4] and Michael Gnant[1] for the Austrian Breast and Colorectal Cancer Study Group

Abstract

Purpose: To determine the effects of anemia on local relapse-free, relapse-free, and overall survival (LRFS, RFS, and OS, respectively) in premenopausal, primary breast cancer patients receiving adjuvant polychemotherapy, and to determine which conventional prognostic factors affected these outcomes.

Experimental Design: Four hundred twenty-four premenopausal patients with early-stage primary breast cancer and hormone receptor–expressing tumors were treated with i.v. cyclophosphamide/methotrexate/5-fluorouracil (CMF) polychemotherapy as part of an adjuvant phase III trial (Austrian Breast and Colorectal Cancer Study Group Trial 5). The influence of anemia (hemoglobin <12 g/dL) on LRFS, RFS, and OS was evaluated in a retrospective analysis.

Results: Of 424 patients, 77 (18.2%) developed anemia on CMF chemotherapy. After a median follow-up time of 5 years, 8.9% of nonanemic patients had local relapse compared with 19.6% of anemic patients ($P = 0.0006$). Although mastectomy was associated with anemia (26% versus 13.7% in breast conserving surgery; $P = 0.002$), multivariate analysis did not show mastectomy per se to be a significant risk factor for LRFS. Age, lymph node status, and hemoglobin had an independent significant influence on LRFS ($P < 0.005$). Anemic patients had a relative risk of 2.96 (95% confidence interval, 1.41-6.23) for developing local relapse in comparison with nonanemic patients.

Conclusion: Premenopausal breast cancer patients who developed anemia during the CMF regimen had significantly worse LRFS. In Austrian Breast and Colorectal Cancer Study Group Trial 5, anemia may have contributed to an almost doubled incidence of local recurrence in the chemotherapy arm. Molecular targets associated with tumor hypoxia and distinct from erythropoiesis should receive further attention in experimental and clinical settings.

Anemia is a syndrome that occurs frequently in cancer patients undergoing adjuvant therapy. In adjuvant breast cancer patients, anemia is unlikely to result from the disease itself (anemia of chronic disease) but is more likely to originate from a combination of (*a*) predisposing factors (e.g., iron deficiency) and (*b*) adjuvant therapy. The combination of blood loss during surgery and low hemoglobin (Hb) levels, induced through chemotherapy and radiotherapy, may lead to a substantial incidence of anemia. In Austria, the incidence of anemia in primary, nonmetastatic breast cancer patients undergoing (non–platinum based) multiagent chemotherapy has been studied in a prospective chart review (1) carried out in 47 centers of surgical, gynecologic, and medical oncology. The total incidence of anemia (<12 g/dL) was close to 60% during adjuvant therapy. After surgery, 28.7% of patients were anemic. Of patients with Hb levels ≥12 g/dL after surgery, 42% developed anemia during chemotherapy. The European Cancer Anemia Survey (2) included more than 3,000 breast cancer patients and found similar results. Of note, only 26% in the European Cancer Anemia Survey and 18.7% in the Austrian study received anemia treatment. In summary, the incidence of anemia in breast cancer patients under adjuvant therapy is high and the proportion of patients receiving treatment is small.

Authors' Affiliations: Departments of [1]Surgery and [2]Gynecology, [3]Medical Department, and [4]Department of Radiotherapy, Medical University Vienna; [5]Department of Gynecology and Obstetrics, Lainz Hospital; [6]Department of Surgery, Hanusch Medical Center, Vienna, Austria; [7]Third Medical Department with Hematology and Oncology, Private Medical University Hospital, Salzburg, Austria; [8]Medical Department, Graz University, Graz, Austria; [9]Department of Surgery, Wiener Neustadt Hospital, Wiener Neustadt, Austria; and [10]Department of Internal Medicine 3, AKH-Linz, Linz, Austria

Received 8/22/07; revised 10/15/07; accepted 1/16/08.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Requests for reprints: Peter Dubsky, Department of Surgery, Medical University Vienna, AKH-Wien, Währingerstr. 18-20, Vienna A-1090, Austria. Phone: 43-1-40400/5621; Fax: 43-1-40400/6918; E-mail: peter.dubsky@meduniwien.ac.at.

doi:10.1158/1078-0432.CCR-07-2068

Anemia has been shown not only to be highly associated with patient energy levels and quality of life scores (3) but also to have prognostic value in several types of cancer (4) including breast cancer (5). Pretreatment Hb levels have also been shown to be predictive of treatment outcomes in chemotherapy, radiotherapy, and/or radiochemotherapy in patients with cancer of the head and neck (6), uterine cervix (7, 8), and prostate (9). In early breast cancer, few clinical reports are indicative of a negative predictive value of anemia with regard to response to radiotherapy (10) and chemotherapy (11, 12).

Several experimental studies suggest that anemia leads to a higher degree of hypoxia (13, 14) in tumor than would be expected for nonneoplastic tissues. Low levels of tissue oxygen tension (pO_2) induce cell signaling through the AKT-mammalian target of rapamycin, thus leading to the up-regulation of hypoxia-inducible factor 1α. In breast cancer (15), as in other tumors (16), this has been shown to promote tumor growth and induce resistance to radiation and chemotherapy (17). In summary, clinical and experimental data support the notion that anemia has profound effects on the prognosis of early breast cancer and may interact with treatment regimens.

As a consequence, a number of prospective randomized trials (reviewed in ref. 18) and retrospective meta-analyses (19) have been initiated to establish a link between the treatment of anemia using erythropoiesis-stimulating agents and the improvement of cancer patient outcome. The results have been far from encouraging. Indeed, in metastatic breast cancer, the "BEST" trial (20) had to be stopped early. The early part of survival curves showed an increased risk of death from cancer in the experimental arm, suggestive of enhanced tumor growth. In summary, anemia remains to be of profound biological importance with regard to prognostic and predictive value in several types of solid organ cancer, but treatment strategies other than erythropoiesis should be pursued.

In 1990, the Austrian Breast and Colorectal Cancer Study Group (ABCSG) initiated a prospective, randomized clinical trial in premenopausal breast cancer patients with positive estrogen and/or progesterone receptor status. The aim of this trial was to evaluate the efficacy of an adjuvant hormonal treatment arm consisting of gonadotropin-releasing hormone analogue combined with tamoxifen compared with a standard treatment arm, which consisted of six cycles of the cyclophosphamide/methotrexate/5-fluorouracil (CMF) polychemotherapy regimen. Overall, this trial showed a superiority of the endocrine treatment as opposed to CMF (21).

As part of this trial, serum blood Hb levels were collected throughout the treatment and follow-up periods. In the chemotherapy arm, 18% of patients showed Hb levels <12 g/dL during the first 3 months postoperatively. Of all patients treated with endocrine therapy, <1% showed a record of anemia within the same period, suggesting a greater effect of polychemotherapy on red blood counts than hormonal therapy. Furthermore, the number of local relapses in patients undergoing chemotherapy was almost twice as high (42 in the CMF arm versus 24 local relapses in the endocrine arm). This translated into a significantly different local relapse rate of 8% versus 5% ($P < 0.01$) between treatment groups.

In the current analysis of prospectively collected data, we have evaluated the effect of anemia on local relapse-free survival (LRFS), recurrence-free survival (RFS), and overall survival (OS) in patients undergoing CMF therapy. Anemia seems to be an independent prognostic factor with regard to local control of breast cancer. Although treatment strategies involving erythropoiesis are no longer valid, molecular targets of tumor hypoxia merit further investigation.

Patients and Experimental Design

Between 1990 and 1999, a total of 1,099 premenopausal patients with primary breast cancer were included in a prospective, randomized, multicenter, phase III trial of the ABCSG Trial 5. Of these patients, 523 were randomized to the polychemotherapy arm consisting of six cycles of i.v. CMF (cyclophosphamide 600 mg/m^2, methotrexate 40 mg/m^2, and 5-fluorouracil 600 mg/m^2) on days 1 and 8 every 4 weeks. All trial patients undergoing breast-conserving surgery received mandatory radiotherapy, which was optional in women who underwent modified radical mastectomy. The sandwich technique was used with irradiation conducted after the first three cycles of CMF. Radiation therapy consisted of external irradiation of the breast with ~50 cGy and a boost irradiation of an additional 8 to 12 cGy of the tumor bed.

Study design, patient eligibility, and patient evaluation. All details on the design of ABCSG Trial 5, patient eligibility for the trial, and patient evaluation have previously been published (21). ABCSG Trial 5 was a prospective, randomized, multicenter study conducted in Austria that compared the effectiveness of endocrine treatment with that of standard chemotherapy regimens (in 1990: CMF) in endocrine-responsive, premenopausal women.

Eligibility for this analysis included all exclusion and inclusion criteria of ABCSG Trial 5. For the current retrospective study of the data, patients who did not receive at least three cycles of CMF, or in whom no Hb levels were documented before the start of chemotherapy, were excluded from the analysis.

Patient follow-up in ABCSG Trial 5 has previously been described (21). Patients' first relapse, local recurrence, and cancer in the opposite breast served as primary end points for RFS, and death served as the primary end point for OS. Whenever possible, local or regional relapses and contralateral incidences required histologic confirmation. Relapses in supraclavicular lymph nodes were classified as distant metastases. Survival parameters were calculated as the time between date of primary surgery and date of histologic diagnosis of local relapse, relapse, or death.

Anemia was defined as the incidence of at least one serum Hb level <12 g/dL during the period of adjuvant chemotherapy through the first follow-up date 3 months after the end of adjuvant treatment. Serum Hb levels were determined before each cycle of adjuvant polychemotherapy and at the time of the first follow-up visit.

Statistical analysis. Frequency distributions (patient characteristics) were analyzed using the χ^2 test. Serum Hb was analyzed as a binary variable; values of <12 g/dL were defined as anemia. Univariate analysis of patient LRFS, RFS, and OS was done using Kaplan-Meier analysis, and survival curves were compared using the log-rank test. A Cox proportional hazards regression model was used to identify independent prognostic factors including age, stage of disease, axillary lymph node status, estrogen and progesterone receptor status, type of surgery, postoperative irradiation, histologic grading, and anemia.

Results

A Hb level <12 g/dL occurred in a total of 18% of patients in the chemotherapy arm and was a very rare event (<1%) in the hormonal treatment arm. Because treatment groups were assigned by prospective, adaptive randomization and patient characteristics (including the type of surgery and the use of radiotherapy) were well balanced between the two groups, the inclusion of polychemotherapy within the treatment regimen was most likely responsible for the difference in anemia rates. Because univariate analysis gave no indication of differential

Table 1. Patient characteristics by anemia status during treatment and follow-up

	N = 424	Hb ≥12 g/dL	Hb <12 g/dL	χ^2	*P*
		n = 347 (81.8%)	*n* = 77 (18.2%)		
Age					
<35 y	26 (6.1%)	80.8%	19.2%	0.021	0.884
≥35 y	398 (93.9%)	81.9%	18.1%		
Tumor stage					
T_1	239 (56.4%)	84.1%	15.9%	3.217	0.200
T_2	167 (39.4%)	77.8%	22.2%		
T_3	18 (4.2%)	88.9%	11.1%		
Axillary lymph nodes					
Negative	204 (48.1%)	82.4%	17.6%	0.105	0.991
Positive (1-3 nodes)	150 (35.4%)	81.3%	18.7%		
Positive (4-10 nodes)	58 (13.7%)	81.0%	19.0%		
Positive (>10 nodes)	12 (2.8%)	83.3%	16.7%		
Histologic grading					
G1, G2, or unknown	308 (72.6%)	79.7%	20.3%	3.266	0.071
G3	116 (27.4%)	87.3%	12.7%		
Estrogen receptor status					
Negative	25 (5.9%)	88.0%	12.0%	0.867	0.648
Positive	294 (69.3%)	81.0%	19.0%		
Strongly positive	105 (24.8%)	82.9%	17.1%		
Progesterone receptor status					
Negative	53 (12.5%)	81.1%	18.9%	0.516	0.773
Positive	230 (54.2%)	83.0%	17.0%		
Strongly positive	141 (33.3%)	80.1%	19.9%		
Type of surgery					
Breast-conserving surgery	270 (63.7%)	86.3%	13.7%	9.934	0.002*
Modified radical mastectomy	154 (36.3%)	74.0%	26.0%		
Radiotherapy					
No	127 (30.0%)	72.4%	27.6%	10.776	0.001*
Yes	297 (70.0%)	85.9%	14.1%		

*Statistically significant.

outcome of anemic patients in the endocrine treatment arm, only the CMF arm was further analyzed for the effect of anemia on survival.

Patients who did not receive at least three cycles of the CMF regimen, or in whom no serum Hb level was documented at the beginning of polychemotherapy, were excluded from this analysis (n = 81). Of the remaining 442 patients, no serum Hb level was available between cycles 3 and 6 in 9 patients; another 9 patients were lost to follow-up after the last cycle of CMF chemotherapy. Therefore, 424 patients were included in this analysis of prospectively collected data.

Patient characteristics are shown in Table 1. Of 424 patients, 77 (18.2%) had at least one serum Hb level <12 g/dL during adjuvant treatment with the CMF regimen or follow-up. The only parameters that correlated with anemia were type of surgery and postoperative irradiation. Patients who had undergone modified radical mastectomy had a significantly higher rate of anemia (26.0%) than patients who had undergone breast-conserving surgery (13.7%; P = 0.002). Because radiotherapy was given largely according to type of surgery, this may have affected the result that patients who did not receive radiotherapy (mostly modified radical mastectomy

Table 2. Correlation of anemia with number of local relapses, relapses, and deaths

	N = 424	Hb ≥12 g/dL	Hb <12 g/dL	χ^2*	*P**
		n = 347	*n* = 77		
Local relapse					
Yes	39	24	15	11.734	0.0006 †
No	385	323	62		
Any relapse					
Yes	96	74	22	2.280	0.1310
No	328	273	55		
Died of disease					
Yes	38	31	7	0.011	0.9162
No	386	316	70		

*Log-rank test.
†Statistically significant.

patients) had a significantly higher risk of anemia (27.6%) than patients who did receive radiotherapy (14.1%; $P = 0.001$).

After a median follow-up time of 61 months, a total of 39 (9.2%) local relapses had occurred among the population of 424 premenopausal breast cancer patients (Table 2). Local relapse was diagnosed in 6.9% of nonanemic patients versus 19.5% of anemic patients ($P = 0.0006$, log-rank test). The overall relapse rate and the number of deaths were equal among anemic and nonanemic patients.

As seen in Fig. 1, LRFS was significantly longer in nonanemic than in anemic patients ($P = 0.0006$, log-rank test). At 5 years, 8.2% of nonanemic versus 19.6% of anemic patients had developed local relapse. RFS and OS curves did not differ significantly between the anemic and nonanemic groups.

According to a multivariate Cox proportional hazards model of all relevant prognostic factors in early-stage breast cancer patients, only age (as a continuous variable), axillary lymph node status, and anemia were shown to be significant prognostic factors for LRFS ($P < 0.005$ for all; Table 3). Anemic patients had a 2.96-fold increased relative risk of developing local relapse compared with nonanemic patients. Radiotherapy, type of surgery, and tumor stage had no significant effect on LRFS. Anemia was not shown to be an independent prognostic factor for RFS or OS (Tables 4 and 5).

Table 3. Multivariate analysis of prognostic factors for LRFS

Prognostic factor	Relative risk (95% confidence interval)	*P*
Age (continuous)	0.816 (0.772-0.862)	0.0001*
Axillary lymph nodes		
Negative		
Positive (1-3 nodes)	2.819 (1.894-4.196)	0.0001*
Positive (4-10 nodes)		
Positive (>10 nodes)		
Anemia		
Hb ≥12 g/dL	2.963 (1.410-6.227)	0.004*
Hb <12 g/dL		
Tumor stage		
T_1		
T_2	1.696 (0.9555-3.011)	0.071
T_3		
Type of surgery		
Breast-conserving surgery	0.372 (0.102-1.350)	0.133
Modified radical mastectomy		
Radiotherapy		
No	0.686 (0.202-2.327)	0.545
Yes		
Estrogen receptor status		
Negative		
Positive	0.816 (0.413-1.611)	0.558
Strongly positive		
Progesterone receptor status		
Negative		
Positive	0.933 (0.534-1.629)	0.806
Strongly positive		
Histologic grading		
G1, G2, or unknown	1.181 (0.569-2.453)	0.655
G3		

*Statistically significant.

Discussion

The results from our prospective, randomized, phase III trial showed that anemia during adjuvant polychemotherapy and radiotherapy in premenopausal primary breast cancer patients has a significant negative effect on LRFS. Local recurrence occurred in 6.9% of nonanemic patients and in 19.5% of patients with Hb levels <12 g/dL. According to the results of our retrospective multivariate analysis, this could not be explained by a correlation between anemia and tumor size, postoperative irradiation, or type of surgery.

In young women with regular menstrual cycles, anemia or at least lower levels of Hb resulting from iron deficiency are common. In the current study, this might be the most common predisposition for developing anemia under adjuvant therapy because anemia caused by stage I to II breast cancer alone is unlikely. Other factors leading to low Hb levels are well distributed between treatment groups due to the prospective randomization procedure. Indeed, there were no differences between the rate of mastectomies and the use of radiotherapy between treatment groups in ABCSG Trial 5 (21). It is thus safe to conclude that the apparent difference in anemia rates was due to the inclusion of polychemotherapy in the treatment regimen.

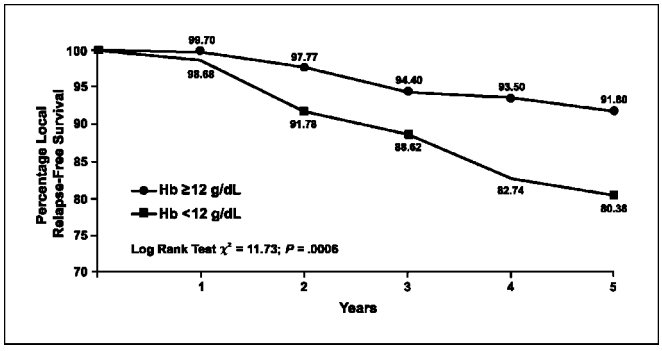

Fig. 1. LRFS for patients with Hb ≥12 g/dL versus Hb <12 g/dL.

In head and neck cancer, the negative effect of low Hb levels on outcome was reported over 20 years ago (22). In breast cancer, Anemia, even in primary operable breast cancer, has prognostic effect in breast cancer patients (2, 5). With regard to the observed effect on LRFS, anemia should be discussed in the context of its interaction with chemotherapy and, maybe most importantly, the influence of anemia on radiotherapy outcome.

With regard to the interaction of chemotherapy and anemia, at least two published reports indicate that patients with Hb levels <12 g/dL have a poor response to preoperative cytotoxic therapy. Bottini et al. (11) reported Hb levels to predict tumor response to primary chemotherapy. In a total of 157 patients treated with either a preoperative CMF + tamoxifen regimen or single agent epirubicin, response at the time of surgery was reduced in patients starting at a cutoff of 12.5 g/dL. The authors suggest an inhibition of antiproliferative activity in anemic patients as a possible mechanism. Beresford et al. made similar observations. Although the influence of anemia (threshold 12 g/dL) did not reach a level of statistical significance in view of response rates, a trend of reduced response in anemic patients was reported. Of note, patients with complete response in this study had a high Hb range between 12.8 and 15.7 g/dL (12).

With regard to the reported data, the influence of Hb levels on the effectiveness of radiotherapy is of particular relevance.

a link between low Hb and response to radiotherapy has also been reported: Kamby et al. studied a cohort of 99 patients with isolated local recurrence after mastectomy. Patients were treated with radical excision and radiotherapy and followed up for survival, interval to second local failure, and distant metastasis. Hemoglobin levels at the time of first recurrence were identified as a prognostic factor of survival (23). Further data linking Hb levels to local control via the interaction with radiotherapy were reported by Henke et al. (10). In this report, low Hb not only influenced disease-free survival but further analysis of the data also suggests that the effect only occurs when radiotherapy was included in the therapeutic regimen.

Finally, a wide range of experimental data serves as a biological basis for the clinical observations summarized above. Tumor hypoxia (most likely aggravated in anemic breast cancer patients; ref. 13) leads to signaling pathways that regulate proliferation, angiogenesis, and apoptosis. These signals are mediated by hypoxia-inducible factors (16). As a consequence, tumor types with a dedifferentiated phenotype may emerge. In breast cancer, this has been established for ductal carcinoma *in situ* lesions (15). Furthermore, hypoxia-inducible factors have been shown to activate pathways associated with stem cell self renewal (Oct4), a finding of utmost importance in view of cancer stem cells (24).

The same line of data linking anemia with tumor hypoxia also explains the interaction of anemia with both chemotherapy and radiotherapy. Low blood flow in tumors can serve as an effective barrier against systemic agents. Effective radiotherapy kills tumor cells by generating reactive oxygen species (25). Thus, in hypoxic tumors, resistance to ionizing radiation can occur.

Experimental advances in the description of molecular pathways associated with tumor hypoxia have identified several new targets for therapy (26). Currently, several small molecule inhibitors of hypoxia-inducible factor-1α activity, although none with specificity for hypoxia-inducible factor 1, are under experimental investigation or moving toward clinical trials (27).

Both clinical observation and experimental data have inspired a series of prospectively randomized trials in which erythropoietin-stimulating agents have been combined with chemotherapy and/or radiotherapy. The disappointing results from these trials have recently been reviewed and commented on (18). As a consequence, the Food and Drug Administration has issued an alert describing an increased risk for thromboembolic disease, promotion of tumor growth, and decreased survival due to erythropoiesis-stimulating agent treatment.[11]

The current report identifies treatment-associated anemia in early breast cancer as an important factor in local tumor

Table 4. Multivariate analysis of prognostic factors for RFS

Prognostic factor	Relative risk (95% confidence interval)	*P*
Age (continuous)	0.893 (0.864-0.924)	0.0001*
Axillary lymph nodes		
Negative	2.461 (1.916-3.159)	0.0001*
Positive (1-3 nodes)		
Positive (4-10 nodes)		
Positive (>10 nodes)		
Anemia		
Hb ≥12 g/dL	1.299 (0.788-2.140)	0.305
Hb <12 g/dL		
Tumor stage		
T_1	1.186 (0.831-1.693)	0.348
T_2		
T_3		
Type of surgery		
Breast-conserving surgery	1.615 (0.813-3.208)	0.171
Modified radical mastectomy		
Radiotherapy		
No	1.216 (0.636-2.328)	0.554
Yes		
Estrogen receptor status		
Negative	0.865 (0.569-1.313)	0.495
Positive		
Strongly positive		
Progesterone receptor status		
Negative	0.719 (0.514-1.006)	0.054
Positive		
Strongly positive		
Histologic grading		
G1, G2, or unknown	1.181 (0.569-2.453)	0.650
G3		

*Statistically significant.

Table 5. Multivariate analysis of prognostic factors for OS

Prognostic factor	Relative risk (95% confidence interval)	*P*
Age (continuous)	0.958 (0.910-1.008)	0.097
Axillary lymph nodes		
Negative	2.488 (1.691-3.660)	0.0001*
Positive (1-3 nodes)		
Positive (4-10 nodes)		
Positive (>10 nodes)		
Anemia		
Hb ≥12 g/dL	0.910 (0.388-2.137)	0.829
Hb <12 g/dL		
Tumor stage		
T_1	1.377 (0.781-2.427)	0.269
T_2		
T_3		
Type of surgery		
Breast-conserving surgery	1.395 (0.483-4.029)	0.539
Modified radical mastectomy		
Radiotherapy		
No	1.056 (0.389-2.868)	0.915
Yes		
Estrogen receptor status		
Negative	0.733 (0.377-1.427)	0.361
Positive		
Strongly positive		
Progesterone receptor status		
Negative	1.245 (0.743-2.089)	0.406
Positive		
Strongly positive		
Histologic grading		
G1, G2, or unknown	1.578 (0.798-3.119)4	0.190
G3		

*Statistically significant.

[11] http://www.fda.gov/cder/drug/infopage/RHE/default.htm

control. In view of the recent pitfalls in the treatment of cancer-associated anemia, the use of erythropoiesis-stimulating agents can hardly be recommended as a viable treatment option. Molecular targets associated with tumor hypoxia and distinct from erythropoiesis merit further experimental and clinical investigation.

Appendix

Members of the Austrian Breast and Colorectal Cancer Study Group who participated in Trial 5 were as follows:

M. Gnant, D. Kandioler, M. Schmidinger, B. Gebhard, S. Taucher, P. Dubsky (Departments of Surgery, Medical University of Vienna, Vienna)

G. Steger, G. Altorjai, R. Bartsch. U. Pluschnig, C. Wenzel, C. Zielinski (Department of Internal Medicine I, Division of Oncology, Medical University of Vienna, Vienna)

P. Mayer, C. Menzel, B. Mlineritsch, C. Rass, R. Reitsamer, G. Russ (Third Medical Department and Department of Special Gynecology, Salzburg Hospital, Salzburg)

T. Bauernhofer, H.-J. Mischinger, M. Schmid, M. Smola, P. Steindorfer, H. Stöger (Departments of Internal Medicine and Surgery, Graz University, and Second Department of Surgery, Graz Hospital, Graz)

E. Asseryanis, A. Galid, R. Möslinger-Gehmayr, M. Seifert (Department of Special Gynecology, Vienna University, Vienna);.

D. Depisch, K. Haider, W. Kwasny, A. Lenauer, T. Payrits (Department of Surgery, Wiener Neustadt Hospital, Wiener Neustadt)

M. Fridrik, R. Greul, G. Hochreiner, G. Wahl (Department of Internal Medicine 3, AKH-Linz, Linz)

G. Jatzko, V. Wette (Department of Surgery, Sankt Veit Hospital, Sankt Veit)

H. Spoula, M. Stierer (Department of Surgery, Hanusch Hospital, Vienna)

U. Schmidbauer, M. Wunderlich (Department of Surgery, Barmherzige Schwestern Hospital, Vienna)

F. Hofbauer, M. Lang (Department of Surgery, Oberpullendorf Hospital, Oberpullendorf)

P. Kier, K. Renner (Second Medical Department and Department of Surgery, Sozialmedizinisches Zentrum Ost Hospital, Vienna)

R. Kocher, F. Stangl (Department of Surgery, Leoben Hospital, Leoben)

G. Luschin-Ebengreuth, R. Winter (Department of Gynecology, Graz University, Graz)

W. Schennach, H. Zoller (Department of Surgery, Zams Hospital, Zams)

F. Kugler, C. Tausch (Department of Surgery, Barmherzige Schwestern Hospital, Linz)

E. Hanzal, C. Sam (Department of Gynecology, Vienna University, Vienna)

A. Haid, R. Köberle-Wührer (Department of Surgery, Feldkirch Hospital, Feldkirch)

W. Döller, E. Melbinger (Department of Surgery, Wolfsberg Hospital, Wolfsberg)

J. Berger, R. Lenzhofer (Medical Department, Schwarzach Hospital, Schwarzach)

H. Ludwig, P. Sagaster (First Medical Department, Wilhelminenspital, Vienna)

G. Reiner, D. Semmler (Department of Surgery, Mistelbach Hospital, Mistelbach)

J. Omann (Department of Surgery, Klagenfurt Hospital, Klagenfurt)

W. Neunteufel (Department of Gynecology, Dornbirn Hospital, Dornbirn).

References

1. Denison U, Baumann J, Peters-Engl C, et al. Incidence of anaemia in breast cancer patients receiving adjuvant chemotherapy. Breast Cancer Res Treat 2003; 79:347–53.
2. Birgegard G, Aapro MS, Bokemeyer C, et al. Cancer-related anemia: pathogenesis, prevalence and treatment. Oncology 2005;68:3–11.
3. Groopman JE, Itri LM Chemotherapy-induced anemia in adults: incidence and treatment. J Natl Cancer Inst 1999;91:1616–34.
4. Caro JJ, Salas M, Ward A, Goss G. Anemia as an independent prognostic factor for survival in patients with cancer: a systemic, quantitative review. Cancer 2001;91:2214–21.
5. Boehm DU, Lebrecht A, Schmidt M, et al. Prognostic impact of haemoglobin levels in breast cancer. Anticancer Res 2007;27:1223–6.
6. Hu K, Harrison LB. Impact of anemia in patients with head and neck cancer treated with radiation therapy. Curr Treat Options Oncol 2005;6:31–45.
7. Choi YS, Yi CM, Sin JI, Ye GW, Shin IH, Lee TS. Impact of hemoglobin on survival of cervical carcinoma patients treated with concurrent chemoradiotherapy is dependent on lymph node metastasis findings by magnetic resonance imaging. Int J Gynecol Cancer 2006;16:1846–54.
8. Grogan M, Thomas GM, Melamed I, et al. The importance of hemoglobin levels during radiotherapy for carcinoma of the cervix. Cancer 1999;86:1528–36.
9. Dunphy EP, Petersen IA, Cox RS, Bagshaw MA. The influence of initial hemoglobin and blood pressure levels on results of radiation therapy for carcinoma of the prostate. Int J Radiat Oncol Biol Phys 1989;16:1173–8.
10. Henke M, Sindlinger F, Ikenberg H, Gerds T, Schumacher M. Blood hemoglobin level and treatment outcome of early breast cancer. Strahlenther Onkol 2004;180:45–51.
11. Bottini A, Berruti A, Brizzi MP, et al. Pretreatment haemoglobin levels significantly predict the tumour response to primary chemotherapy in human breast cancer. Br J Cancer 2003;89:977–82.
12. Beresford MJ, Burcombe R, Ah-See ML, Stott D, Makris A. Pre-treatment haemoglobin levels and the prediction of response to neoadjuvant chemotherapy in breast cancer. Clin Oncol (R Coll Radiol) 2006;18: 453–8.
13. Vaupel P, Mayer A, Briest S, Hockel M. Oxygenation gain factor: a novel parameter characterizing the association between hemoglobin level and the oxygenation status of breast cancers. Cancer Res 2003;63:7634–7.
14. Vaupel P, Mayer A, Hockel M. Impact of hemoglobin levels on tumor oxygenation: the higher, the better? Strahlenther Onkol 2006;182:63–71.
15. Helczynska K, Kronblad A, Jogi A, et al. Hypoxia promotes a dedifferentiated phenotype in ductal breast carcinoma *in situ*. Cancer Res 2003;63:1441–4.
16. Harris AL. Hypoxia-a key regulatory factor in tumour growth. Nat Rev Cancer 2002;2:38–47.
17. Vaupel P, Mayer A. Hypoxia and anemia: effects on tumor biology and treatment resistance. Transfus Clin Biol 2005;12:5–10.
18. Khuri FR. Weighing the hazards of erythropoiesis stimulation in patients with cancer. N Engl J Med 2007;356:2445–8.
19. Bohlius J, Wilson J, Seidenfeld J, et al. Recombinant human erythropoietins and cancer patients: updated meta-analysis of 57 studies including 9353 patients. J Natl Cancer Inst 2006;98:708–14.
20. Leyland-Jones B, Semiglazov V, Pawlicki M, et al. 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 2005;23:5960–72.
21. Jakesz R, Hausmaninger H, Kubista E, et al. Randomized adjuvant trial of tamoxifen and goserelin versus cyclophosphamide, methotrexate, and fluorouracil: evidence for the superiority of treatment with endocrine blockade in premenopausal patients with hormone-responsive breast cancer—Austrian Breast and Colorectal Cancer Study Group Trial 5. J Clin Oncol 2002;20:4621–7.
22. Overgaard J, Hansen HS, Jorgensen K, Hjelm Hansen M. Primary radiotherapy of larynx and pharynx carcinoma-an analysis of some factors influencing local control and survival. Int J Radiat Oncol Biol Phys 1986;12:515–21.
23. Kamby C, Sengelov L. Survival and pattern of failure following locoregional recurrence of breast cancer. Clin Oncol (R Coll Radiol) 1999;11:156–63.
24. Keith B, Simon MC. Hypoxia-inducible factors, stem cells, and cancer. Cell 2007;129:465–72.
25. Vaupel P, Thews O, Hoeckel M. Treatment resistance of solid tumors: role of hypoxia and anemia. Med Oncol 2001;18:243–59.
26. Semenza GL. Targeting HIF-1 for cancer therapy. Nat Rev Cancer 2003;3:721–32.
27. Patiar S, Harris AL. Role of hypoxia-inducible factor-1α as a cancer therapy target. Endocr Relat Cancer 2006;13:S61–75.