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ORIGINAL ARTICLE

# Anemia during adjuvant non-taxane chemotherapy for early breast cancer: Incidence and risk factors from two trials of the International Breast Cancer Study Group

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**Abstract**
*Goal of the work* Anemia is a common side effect of chemotherapy. Limited information exists about its incidence and risk factors. The objective of this study was to evaluate the incidence of anemia and risk factors for anemia occurrence in patients with early breast cancer who received adjuvant chemotherapy.

The authors represent the International Breast Cancer Study Group.

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*Materials and methods* We evaluated risk factors for anemia in pre- and post/perimenopausal patients with lymph node-positive early breast cancer treated with adjuvant chemotherapy in two randomized trials. All patients received four cycles of doxorubicin and cyclophosphamide (AC) followed by three cycles of cyclophosphamide, methotrexate, fluorouracil (CMF). Anemia incidence was related to baseline risk factors. Multivariable analysis used logistic and Cox regression.
*Main results* Among the 2,215 available patients, anemia was recorded in 11% during adjuvant chemotherapy. Grade 2 and 3 anemia occurred in 4 and 1% of patients, respectively. Pretreatment hemoglobin and white blood cells (WBC) were significant predictors of anemia. Adjusted odds ratios (logistic regression) comparing highest versus lowest quartiles were 0.18 ($P<0.0001$) for hemoglobin and 0.52 ($P=0.0045$) for WBC. Age, surgery type, platelets, body mass index, and length of time from surgery to chemotherapy were not significant predictors. Cox regression results looking at time to anemia were similar.
*Conclusions* Moderate or severe anemia is rare among patients treated with AC followed by CMF. Low baseline hemoglobin and WBC are associated with a higher risk of anemia.

**Keywords** Adjuvant therapy · Adverse event · Anemia · Breast cancer · Chemotherapy

## Introduction

Anemia is a common complication in cancer patients, occurring in more than 50% of patients as a result of pathogenetic factors such as the disease itself and its complications and treatment [3]. Some patients may be anemic before treatment, but the incidence increases during subsequent chemotherapy cycles and depends on the primary tumor site, previous myelosuppressive treatment, type of chemotherapy, schedule, and duration [6, 12, 26]. Anemia represents a significant cause of morbidity [3] with a broad spectrum of clinical manifestations such as fatigue, weakness, respiratory distress, and variable effects on physical and cognitive capacities; it is a frequent complication in patients with metastatic breast cancer, particularly when treated with taxane-based regimens [12, 26]. However, data about anemia in patients with early breast cancer treated with adjuvant chemotherapy are more limited, possibly due to underestimation and under-treatment of anemia [9, 18, 26]. In a large study designed to evaluate serious adverse effects (SAE) experienced by women younger than 63 years and receiving chemotherapy for recently diagnosed breast cancer (metastatic or not), 2.2% of patients had a SAE because of anemia or transfusions. Anemia was the fifth most common cause of SAE after fever-infection (8.4%), neutropenia–thrombocytopenia (5.5%), dehydration–electrolyte disorders (2.5%), and nausea–emesis–diarrhea (2.4%) [14]. An even higher rate (9.2%) of hospitalization due to anemia after chemotherapy was reported in women with breast cancer older than 65 years [11]. In past decades, red blood cell transfusion was the mainstay treatment for cancer-related anemia. Transfusions are effective in ameliorating symptoms, but they are associated with short-lived benefits and possible risks and are generally reserved for patients with more severe anemia or symptoms. The advent of erythropoietins (EPOs) generated a new awareness about anemia in cancer patients, showing that, even when mild or moderate, anemia may impair quality of life (QoL) [4]. Associations between hemoglobin (Hgb) level and QoL parameters have been reported, indicating the importance of maintaining near to normal Hgb during treatment [8]. EPOs increase Hgb and reduce the need for red blood transfusions in cancer patients receiving chemotherapy [2, 5].

Identification of patients at risk for anemia and its complications may improve supportive treatment during chemotherapy. This is particularly important for elderly patients for whom the National Cancer Center Network (NCCN) guidelines suggest maintaining hemoglobin level above 12 mg/l [22]. The purpose of this study was to examine the incidence of anemia among a large number of patients with early breast cancer from two International Breast Cancer Study Group (IBCSG) trials who received similar adjuvant chemotherapy and to evaluate risk factors for anemia occurrence.

## Materials and methods

The two IBCSG trials were conducted between 1993 and 1999. The patient populations in IBCSG trials 13–93 and 14–93 consisted of women with node-positive breast cancer considered not suitable for endocrine therapy alone. Trial 13–93 accrued 1,246 patients and evaluated the role of tamoxifen for premenopausal women, comparing a 5-year course versus no endocrine therapy [17], while trial 14–93 accrued 969 patients and compared the estrogen receptor modulators (SERM) toremifene to tamoxifen [16]. The trials were combined to evaluate the role of a treatment-free gap (results not published). Patients on both trials received the same non-taxane chemotherapy consisting of four 21-day courses of AC (doxorubicin 60 mg/m$^2$ and cyclophosphamide 600 mg/m$^2$ intravenously on day 1) or EC (epirubicin 90 mg/m$^2$ and cyclophosphamide 600 mg/m$^2$ intravenously on day 1) followed either immediately or after a16-week gap by three 28-day courses of "classical" CMF (cyclophosphamide at 100 mg/m$^2$ orally on days 1–14, methotrexate at

**Table 1** Baseline characteristics of the patients

| Characteristic | Trial 13–93 (*N*=1,246) Mean (SD) | Trial 14–93 (*N*=969) | All trials (*N*=2,215) |
|---|---|---|---|
| Age (yr) | 43 (6) | 58 (6) | 49 (9) |
| Hgb (g/dl) | 12.9 (1.6) | 13.2 (1.4) | 13.0 (1.5) |
| WBC×1,000 | 7.2 (2.0) | 6.9 (2.5) | 7.1 (2.2) |
| Platelets×1,000 | 278 (77) | 274 (73) | 276 (75) |
| BMI (kg/m$^2$) | 25.0 (4.6) | 27.0 (5.0) | 25.9 (4.9) |
| Weight (kg) | 66 (13) | 69 (13) | 68 (13) |
| Days from surgery to treatment | 29 (9) | 31 (9) | 30 (9) |
| Type of surgery | Number (%) | | |
| Mastectomy | 707 (57) | 560 (58) | 1267 (57) |
| Breast-conserving | 538 (43) | 409 (42) | 947 (43) |

In Trials 13–93 and 14–93, Hgb was missing for 11 and 7 patients, respectively; WBC was missing for 10 and 6 patients, respectively; platelet count was missing for 15 and 6 patients, respectively; BMI was missing for 2 and 3 patients, respectively; weight was missing for 2 and 2 patients, respectively; days from surgery to treatment was missing for 20 and 9 patients, respectively. Type of surgery was missing for 1 patient in trial 13–93. *SD* Standard deviation; *yr* years; *WBC* white blood cells; *BMI* body mass index; *kg* kilograms; *m* meters; *g*/*dl* grams per deciliter; *Hgb* hemoglobin

40 mg/m$^2$ intravenously on days 1 and 8, and 5-fluorouracil at 600 mg/m$^2$ intravenously on days 1 and 8). All randomized patients were included in the present study.

Adequate bone-marrow function [white blood cell (WBC) count >4.0×10$^9$/l and platelet count>100×10$^9$/l] was a required eligibility criterion, while low Hgb was not. Case report forms at baseline collected Hgb level (g/dl). During chemotherapy, case report forms including anemia grade were completed at each cycle of chemotherapy for a total of seven evaluations. In both trials, anemia was defined as Hgb<11 g/dl. The protocol defined three grades of anemia as follows: asymptomatic, Hgb 10–11 g/dl (grade 1); slight symptoms, Hgb 8–10 g/dl (grade 2); symptoms, transfusions required (grade 3). Data on anemia were collected only during the period of treatment administration.

The statistical analysis consisted of first evaluating the crude incidence of anemia (percent of patients with anemia at any time) according to trial, treatment cycle, and grade of anemia. Incidence of anemia was then determined according to the following baseline risk factors: age, Hgb level (absolute value, g/dl), type of surgery [mastectomy versus breast-conserving surgery (BCS)], WBC count, platelet count, body mass index (BMI), body weight, and the number of days from surgery until the start of chemotherapy. Hgb level, WBC count, platelet count, BMI, weight, and interval from surgery to chemotherapy were grouped into quartiles. Age was grouped in 5-year intervals. The crude incidence of anemia was then determined for each risk factor according to trial and randomized treatment group. The chi square test was used to evaluate the association between each risk factor and the occurrence of any grade of anemia.

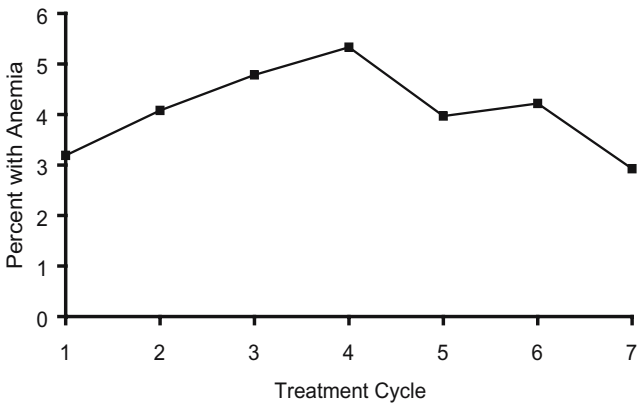


**Fig. 1** Incidence of anemia according to treatment cycle. The cycle-specific incidence rates were computed as the percent of patients experiencing any grade of anemia among those who received the cycle of treatment

Data from both trials were then combined, and overall anemia incidence rates were determined according to the levels of each risk factor, and the chi square test was used to evaluate any association. Time to anemia was defined as the treatment cycle number in which any anemia was first observed. Incidence curves, based on the product-limit method, were determined for each level of each risk factor. The log-rank test was used to evaluate association. Multiple logistic regression was used to evaluate the joint association between the risk factors and the occurrence of any grade of anemia. Odds ratios were determined, along with 95% confidence intervals, based on the fitted model. The analysis was conducted with adjustment for trial and randomized treatment, and each baseline factor was considered separately. A stepwise selection procedure was then used to develop a multivariable model. Factors with a *P* value (based on a Wald test) less than 0.05 were included in the model. Risk factors having a *P* value>0.10 were removed. Similar analyses were performed using Cox

**Table 2** Logistic regression analysis of any grade of anemia by baseline factors

| Variable | *N* | Anemia incidence (%) | Odds ratio | 95% CI | *P* value |
|---|---|---|---|---|---|
| Age (yr) | | | | | |
| ≤39 | 331 | 11 | 1.00 | – | 0.18 |
| 40–44 | 352 | 11 | 1.18 | 0.72–1.92 | |
| 45–49 | 471 | 8 | 0.75 | 0.46–1.23 | |
| 50–54 | 380 | 11 | 1.08 | 0.66–1.76 | |
| 55–59 | 332 | 12 | 1.17 | 0.71–1.93 | |
| 60–64 | 223 | 14 | 1.49 | 0.88–2.53 | |
| 65+ | 126 | 13 | 1.46 | 0.77–2.72 | |
| Hgb (g/dl) | | | | | |
| ≤12.1 | 527 | 18 | 1.00 | – | <0.0001 |
| 12.2–13.0 | 519 | 13 | 0.68 | 0.48–0.96 | |
| 13.1–13.8 | 543 | 9 | 0.42 | 0.29–0.62 | |
| 13.9+ | 608 | 4 | 0.18 | 0.11–0.29 | |
| Type of surgery | | | | | |
| Mastectomy | 1,267 | 10 | 1.00 | – | 0.78 |
| BCS | 947 | 11 | 1.04 | 0.79–1.37 | |
| WBC × 1,000 | | | | | |
| ≤5.5 | 526 | 14 | 1.00 | – | 0.0062 |
| 5.6–6.6 | 526 | 11 | 0.75 | 0.52–1.09 | |
| 6.7–8.1 | 582 | 12 | 0.79 | 0.55–1.13 | |
| 8.2+ | 565 | 7 | 0.48 | 0.32–0.73 | |
| Platelets × 1,000 | | | | | |
| ≤224 | 548 | 13 | 1.00 | – | 0.27 |
| 225–267 | 538 | 9 | 0.73 | 0.49–1.07 | |
| 268–316 | 552 | 9 | 0.72 | 0.49–1.06 | |
| 317+ | 556 | 11 | 0.88 | 0.61–1.26 | |
| BMI ($kg/m^2$) | | | | | |
| ≤22.3 | 546 | 12 | 1.00 | | 0.44 |
| 22.4–24.9 | 557 | 11 | 0.94 | 0.65–1.36 | |
| 25.0–28.4 | 550 | 11 | 0.90 | 0.62–1.31 | |
| 28.5+ | 557 | 9 | 0.73 | 0.49–1.08 | |
| Weight (kg) | | | | | |
| ≤57 | 488 | 13 | 1.00 | – | 0.12 |
| 58–64 | 534 | 12 | 0.93 | 0.64–1.36 | |
| 65–74 | 618 | 10 | 0.72 | 0.49–1.05 | |
| 75+ | 571 | 9 | 0.67 | 0.45–0.99 | |
| Days from surgery to treatment | | | | | |
| ≤23 | 540 | 12 | 1.00 | – | 0.52 |
| 24–29 | 424 | 11 | 0.89 | 0.59–1.34 | |
| 30–35 | 641 | 10 | 0.78 | 0.53–1.13 | |
| 36+ | 581 | 12 | 0.99 | 0.69–1.43 | |

*P* values are based on Wald chi square tests and are adjusted for trial and randomized treatment group.
*CI* Confidence interval; *yr* years; *BCS* breast-conserving surgery; *WBC* white blood cells; *BMI* body mass index; *kg* kilograms; *m* meters; *g/dl* grams per deciliter; *Hgb* hemoglobin

regression to evaluate the time to anemia. Any patient with missing data for any of the risk factors was excluded from the multivariable analyses. A two-sided *P* value less than 0.05 was considered statistically significant.

## Results

Data were available from a total of 2,215 patients in IBCSG trials 13–93 and 14–93. Table 1 describes the baseline characteristics of the patients. About a quarter of the patients had a baseline Hgb level<12.1 g/dl, but this percentage differed slightly among the trials: 27% in trial 13–93 and 19% in trial 14–93, probably reflecting higher prevalence of iron deficiency anemia among premenopausal women in trial 13–93. The rates of protocol-defined anemia of any grade (i.e., Hgb<11.0 g/dl) at baseline were 9% in trial 13–93 and 5% in trial 14–93, for an overall baseline rate of 7%.

Figure 1 shows the incidence of anemia (any grade) by treatment cycle. Generally, anemia was reported as mild (grade 1) or moderate (grade 2). Overall, there were 238 patients (11%) with at least one report of anemia of any grade occurring during any chemotherapy cycle, and there were 96 (4%) and 16 (1%) patients with grade 2 and grade 3 anemia, respectively, occurring during any treatment

**Table 3** Stepwise logistic regression analysis of any grade of anemia

| Variable | Odds ratio | 95% CI | *P* value |
|---|---|---|---|
| Hgb (g/dl) | | | |
| ≤12.1 | 1.00 | – | <0.0001 |
| 12.2–13.0 | 0.69 | 0.49–0.97 | |
| 13.1–13.8 | 0.43 | 0.29–0.62 | |
| 13.9+ | 0.18 | 0.11–0.29 | |
| WBC×1,000 | | | |
| ≤5.5 | 1.00 | – | 0.021 |
| 5.6–6.7 | 0.82 | 0.56–1.20 | |
| 6.8–8.1 | 0.83 | 0.57–1.19 | |
| 8.2+ | 0.52 | 0.34–0.79 | |

*P* values are based on Wald chi square tests and are adjusted for all factors shown in the table as well as for trial and randomized treatment group.
*CI* Confidence interval; *Hgb* hemoglobin; *WBC* white blood cells; *g/dl* grams per deciliter

cycle. On the whole, the incidence of anemia tended to increase with additional treatment cycles until cycle 4, after which it tended to decrease.

Table 2 shows the incidence of anemia (any grade during any cycle) according to baseline characteristics after pooling the data from the two trials. Univariate analysis found that pretreatment Hgb ($P<0.0001$) and WBC count ($P=0.011$) were significantly associated with the development of anemia. The risk of anemia decreased with increased Hgb and WBC. No other baseline factor was significantly associated with anemia. Similar findings were obtained after adjustment for trial and treatment group (Table 2).

Stepwise logistic regression analysis showed that Hgb and WBC count were jointly significantly associated with anemia occurrence after adjustment for trial and randomized treatment group. Table 3 shows the results of the final model derived by stepwise selection. Similar results were obtained when considering time to first occurrence of anemia of any grade. Table 4 shows the results of the Cox model analysis based on stepwise selection. Fifty-eight patients were excluded from multivariable analyses due to missing data, leaving 2,157 available patients. Of the risk factors investigated, baseline Hgb was most strongly related to anemia. Figure 2 illustrates the cumulative incidence of anemia by quartile of Hgb and treatment cycle.

**Table 4** Stepwise Cox regression analysis of time until any grade of anemia

| Variable | Hazard ratio | 95% CI | *P* value |
|---|---|---|---|
| Hgb (g/dl) | | | |
| ≤12.1 | 1.00 | – | <0.0001 |
| 12.2–13.0 | 0.68 | 0.50–0.93 | |
| 13.1–13.8 | 0.43 | 0.30–0.61 | |
| 13.9+ | 0.19 | 0.12–0.30 | |
| WBC×1,000 | | | |
| ≤5.5 | 1.00 | – | 0.043 |
| 5.6–6.7 | 0.85 | 0.60–1.22 | |
| 6.8–8.1 | 0.86 | 0.62–1.21 | |
| 8.2+ | 0.57 | 0.39–0.84 | |

*P* values are based on Wald chi square tests and are adjusted for all factors shown in the table as well as for trial and randomized treatment group.
*CI* Confidence interval; *Hgb* hemoglobin; *WBC* white blood cells; *g/dl* grams per deciliter

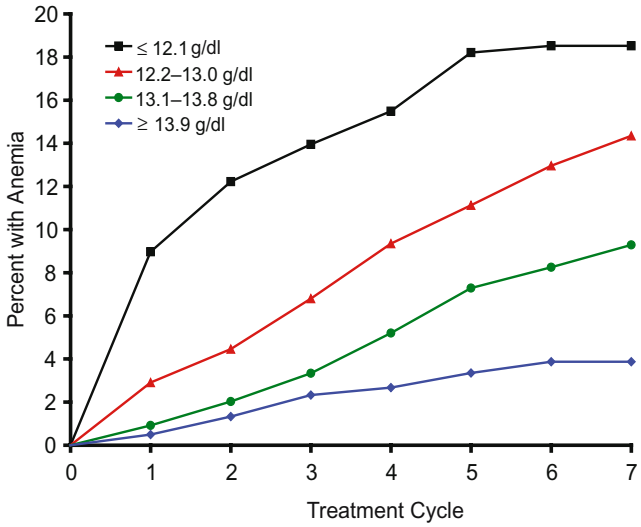


**Fig. 2** Cumulative incidence of anemia by quartile of baseline hemoglobin (g/dl). Cumulative incidence was computed using the product-limit method (log-rank $P<0.0001$)

We also performed the logistic and Cox regression analyses on the subset of patients who were free of protocol-defined anemia at baseline (i.e., Hgb≥11.0 g/dl). Using the same groupings as described above, stepwise logistic regression analysis found that pretreatment Hgb and WBC were significantly associated with anemia ($P<0.0001$ and $P=0.026$, respectively). In addition, type of surgery was found to be significantly associated. Patients receiving BCS were at higher risk of anemia (odds ratio: 1.39; 95% CI: 1.02–1.89; $P=0.036$). Similar results were observed with Cox regression in this subgroup.

## Discussion

Among our patients, prevalence of anemia (Hgb<12 g/dl) after surgery and before chemotherapy was about 25%: similar to other reported series [9,18,26], and was slightly more frequent in premenopausal patients. Possible reasons include iron deficiency and blood loss from surgery or from prolonged or abundant menses [9], while anemia of chronic disease related to cancer should not be a factor in these patients with stage I, II, and III breast cancer. Anemia after surgery and before chemotherapy starting is often neglected, with only 10% of all patients having iron

metabolism evaluated, thus missing the opportunity to detect and treat iron deficiency anemia, an easily treatable condition [18].

During chemotherapy, anemia incidence in our studies was lower than that reported by others [9,18]. In patients without baseline anemia, treated with similar adjuvant regimens, some degree of anemia was recorded in 42% [9] or even 88% [18] of cases after chemotherapy, although only 27% of patients developed moderate to severe anemia [18]. A partial explanation for this difference from other studies may be related to the toxicity grading system used in IBCSG trials: anemia was actually defined as any recorded Hgb level lower than 11 g/dl, while a cut-off of 12 g/dl was defined in other papers [9,18, 26] in conformity to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events version 3.0 (CTCAE) [21]. As most patients on chemotherapy who develop anemia have NCI grade 1 anemia (12–10 g/dl) [18, 26], the IBCSG definition we used would have excluded a considerable number of patients who had Hgb levels between 11 and 12 g/dl.

Incidence of anemia was quite stable through successive cycles of chemotherapy, a finding in agreement with previous reports [26]. Baseline characteristics predictive of anemia during adjuvant chemo-endocrine therapy included pretreatment Hgb and WBC count. In previous studies, prechemotherapy Hgb level was the most commonly reported risk factor for anemia on treatment or requirement for transfusion [1, 6, 9, 18]. Other reported risk factors include age older than 65 [11], hemoglobin decrease during the first month of chemotherapy [6], duration of chemotherapy [6], tumor type [1, 6], previous transfusions [6, 7], platinum-based chemotherapy [1] and platinum pharmacokinetics [23], multiple concurrent chemotherapeutic agents [25], female sex [1], performance status (PS)>1 [24], pretreatment absolute lymphocyte count (ALC) lower than 700/μl [24]. Our data set did not permit us to test all these reported risk factors, but our results are consistent. The low number of patients aged more than 65 years in our series of patients makes the evaluation of age as a risk factor for chemotherapy-induced anemia inconclusive.

Risk models have been developed to predict more accurately the risk of anemia or need for red blood cell transfusion. Ray-Coquard et al. [24] retrospectively identified three independent risk factors for anemia requiring transfusion as PS>1, Hgb<12 g/dl, and ALC≤700/μL. More recently, different prediction models for chemotherapy-induced anemia were developed for patients with breast cancer receiving adjuvant chemotherapy [10] and for patients with non-small lung cancer receiving palliative chemotherapy [27].

Clinical studies and meta-analyses have shown that recombinant EPO may prevent chemotherapy-induced anemia, reducing the need for transfusions and thus improving quality of life parameters [2, 5] with possible improvement in productivity and work attitude in cancer patients receiving chemotherapy. However, the absence of reliable baseline and early treatment factors useful to predict response to EPO [20] and the costs and possible risk [2, 13, 15,19] of these supportive therapies are open questions.

Our study shows that with a non-taxane-based, standard dose, adjuvant chemotherapy, anemia is relatively infrequent and rarely severe. Future studies should attempt to identify those patients at higher risk of severe anemia, with possible improvement in supportive care during adjuvant treatment.

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