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ORIGINAL ARTICLE

Impact of haemoglobin levels during adjuvant chemotherapy on the survival of patients with primary breast cancer

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Abstract
Tumour anaemia is a common symptom in cancer patients, particularly in those receiving chemotherapy. The aim of the current study was to analyse the impact of haemoglobin levels on the prognosis of patients with primary breast cancer receiving adjuvant chemotherapy. A total of 129 patients were available for analysis. The estimated median five-year overall survival rate was 76.6%. Mean Hb prior to primary surgery was 13.8 g/dl (SD 1.09), pre-chemotherapy Hb 12.8 g/dl (SD 1.2), and nadir Hb during chemotherapy 11.0 g/dl (SD1.1), respectively. Hb values were analysed as continuous variables in the Cox model. Survival analyses did not show a correlation between preoperative and pre-chemotherapy Hb levels with patient outcome. However, univariate analysis identified low nadir Hb ($p = 0.008$), larger tumours ($p = 0.042$), and hormone-receptor-negative tumours ($p = 0.022$) to be significantly associated with poor patient survival. This result was persistent when analysis was adjusted for relevant prognostic factors in a multivariate Cox proportional hazards model. Nadir Hb, 1.54-fold increased risk for death (95% CI 1.03–2.32), and tumour size, 3.2-fold increased risk (95% CI 1.17–8.77) remained as independent variables, whereas hormone-receptor status failed to retain significance. The present data showed anaemia during adjuvant chemotherapy to be associated with poor survival in patients with primary breast cancer. Prospective randomized trials are warranted to examine the value of correcting anaemia with regard to improve disease control and survival.

Introduction

Tumour anaemia is a common symptom in cancer patients, particular in those receiving chemotherapy [1]. Chemotherapy-induced anaemia is mainly due to the myelosuppressive effect and differs with the type of antineoplastic drugs. There has been increasing evidence that anaemia leads to impaired tumour oxygenation [2,3] with subsequent radio- and chemo-resistance. Several reports have shown a correlation between low haemoglobin (Hb) levels and impaired disease-free and overall survival in patients with solid malignancies including carcinoma of the uterine cervix and the ovary [4,5]. In addition, pre-treatment Hb has been reported to have an impact on the effectiveness of neoadjuvant chemotherapy in human breast cancer [6], but no data are available regarding the prognostic value of anaemia in the adjuvant setting.

The aim of the current study is to analyse haemoglobin levels at different time points during treatment and the impact of anaemia on the prognosis of patients with primary breast cancer receiving adjuvant chemotherapy.

Material and methods

A total of 129 patients with primary breast cancer were treated with adjuvant cytotoxic chemotherapy at the department of O&G at the General Hospital Lainz between November 1993 and November 2000. This retrospective survey did not include patients treated with neoadjuvant chemotherapy.

The standard surgical treatment consisted of either quadrantectomy with axillary dissection or modified radical mastectomy. Tumours were classified as described by the American Joint Committee on Cancer. Hormone receptor content was determined immunohistochemically. In patients subjected to breast conservation, surgery was followed by local

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irradiation. Chemotherapy consisted of six cycles either CMF (600/40/600) day 1,8 i.v., AC (60/600) or EC (90/600); a few patients were treated with taxane-containing regimens. Hormone-receptor-positive patients received 5 years of 20 mg tamoxifen sequentially. Patients were reviewed every 3 months within the first 3 years of primary surgery, then every 6 months for up to 5 years. Follow up visits consisted of history, physical examination, and haematological tests including tumour markers (CEA, CA 15-3). Mammography and chest x-rays were performed on an annual basis; ultrasonography of the upper abdomen and bone scintigram was performed if tumour relapse was suspected. The primary study endpoints were disease-free (DFS), distant disease-free (DDFS), and overall survival (OS).

A full blood count was determined by venous puncture prior to primary surgery, pre-chemotherapy, and weekly during chemotherapy. The lowest Hb level (nadir Hb) that was observed during chemotherapy was used for statistical analyses. Hb values are given in grams per litre $\times 10^{-2}$ (g/dl).

Survival times were defined as the period between the date of primary surgery and relapse or death (disease-free survival, DFS), distant relapse or death (distant disease-free survival, DDFS), and death (overall survival OS). Survival times of patients still disease free and alive were censored with the last date of follow-up. Survival probabilities were calculated by the product limit method of Kaplan and Meier. The Cox proportional hazards model was used to assess the univariate and partial effects of prognostic factors on survival time. Hb values were expressed as the mean $\pm$ standard deviation (SD) and were entered in the Cox model as continuous variable. All reported p-values are results of two-sided tests. A p-value of equal to or less than 5% was considered statistically significant. The SPSS 10.0.7 statistical software system was used for calculations.

Table I. Patient characteristics.

	n (%)
All pateients	129
Age (mean, SD)	55.4 (SD 11.7)
Tumour size	
<2 cm	68 (52.7)
≥2 cm	61 (47.3)
Grading	
G1, 2	52 (40.3)
G3	60 (46.5)
No data	17 (13.2)
Nodal status	
positive	83 (64.3)
negative	46 (35.7)
ER	
positive	73 (56.6)
negative	51 (39.5)
unknown	5 (3.9)
PR	
positive	71 (55.0)
negative	53 (41.1)
unknown	5 (3.9)
Type of surgery	
BCT	97 (75.2)
MRM	30 (23.3)
Unknown	2 (1.6)
Adjuvant radiotherapy	
Yes	91 (70.5)
No	33 (25.6)
unknown	5 (3.9)
Chemotherapy	
CMF	74 (57.4)
Antracyclin	49 (38.0)
Other	6 (4.6)
Dose-intensity of chemotherapy	
<85%	18 (13.9)
<90%	24 (18.6)
≥90%	105 (81.4)

Results

A total number of 129 women with primary breast cancer receiving adjuvant chemotherapy were evaluable. At the time of analysis, 27 patients had died due to underlying disease. The estimated median five-year rates were DFS 68.4%, DDFS 73.8%, and OS 76.6% respectively.

Surviving patients were followed up for a median of 4.5 years (range 1.9–9.4) estimated from the time of primary surgery. Detailed patients characteristics are given in Table I. Overall mean Hb prior to primary surgery was 13.8 g/dl (SD 1.09), pre-chemotherapy Hb 12.8 g/dl (SD 1.2), and nadir Hb during chemotherapy 11.0 g/dl (SD 1.1), respectively. Three patients were treated with rh-EPO for anaemia during chemotherapy and 1 patient received at least one blood transfusion.

Association of preoperative and pre-chemotherapy Hb levels with prognosis

Survival analyses did not show a correlation between preoperative Hb levels with DFS hazard ratio 0.98 (95% CI 0.71–1.33), DDFS 0.97 (95% CI 0.70–1.37), and OS 1.03 (95% CI 0.73–1.45). Pre-chemotherapy Hb levels also failed to correlate with DFS hazard ratio 1.09 (95% CI 0.83–1.43), DDFS 1.06 (95% CI 0.79–1.45), and OS 1.18 (95% CI 0.85–1.61) respectively.

Association of nadir Hb during chemotherapy with prognosis

Univariate analysis identified nadir Hb as a prognostic factor for overall survival, showing a correlation between anaemia and impaired overall survival hazard ratio of 1.58 (95% CI 1.13–2.22, p = 0.008). The impact of all evaluated factors is given in Table II, showing larger tumours and hormone-receptor negative tumours to be associated with poor survival, whereas nodal status, tumour grading, age, type of surgery, CTX regimen, and CTX dose failed to show significance. For descriptive reasons the nadir Hb was categorized into two groups (Figure 1). Further analysis was performed by entering all prognostic variables as covariates in a Cox proportional hazards model (Table II). Of the variables that showed a significant influence on OS in the univariate analysis, only nadir Hb and tumour size remained as independent variables, whereas receptor status failed to retain significance. Nadir Hb showed a 1.54-fold higher risk (95% CI 1.03–2.32) of dying from breast cancer. Tumours above 2 cm engendered a 3.2-fold increased risk (95% CI 1.17–8.77) of death.

Finally, analysis was extended in respect of DFS and DDFS (Table III). Tumour size and nodal status were independent prognostic factors for DFS hazard ratio 2.94 (95% CI, 1.26–6.84) and 3.22 (95% CI 1.27–8.10), respectively. In contrast, DDFS was significantly associated with nadir Hb (HR 1.54, 95% CI 1.04–2.32) and tumour size (HR 2.94, 95% CI 1.12–7.63), which was in accordance with our findings for OS.

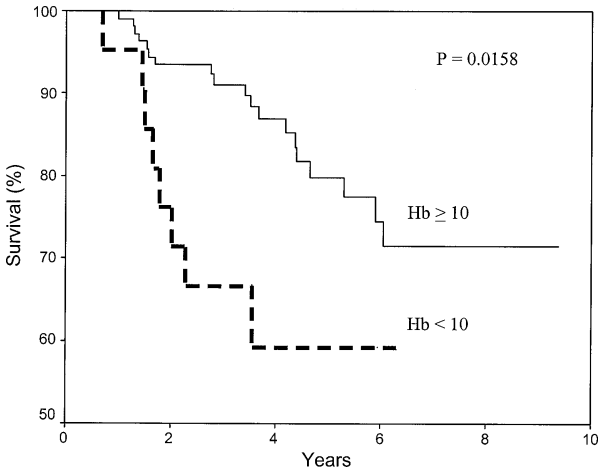

Figure 1. Kalpan–Meier plot: survival according to Hb level (threshold 10 g/dl), log rank test.

Discussion

This is the first study addressing the correlation between Hb levels and survival of patients with primary breast cancer receiving adjuvant chemotherapy. The data provide clear evidence that anaemia during adjuvant chemotherapy is associated with poor survival in patients with primary breast cancer. This is in concordance with findings from studies on other solid tumours showing low Hb levels during concurrent chemo-radiotherapy rather than the Hb level prior to therapy to be more important for local control and survival [7,8], but the exact threshold for "low Hb" remains to be defined. However, our study is the first one that shows the prognostic value of nadir Hb, analysed as continuous variable, during adjuvant cytotoxic therapy in patients with primary breast cancer.

In our series the nadir Hb level during cytotoxic chemotherapy is significantly predictive for DDFS and OS, whereas no effect for DFS (local and distant relapse) is observed. The impact of local relapse might give an explanation for this finding: Radiotherapy for local control in patients treated with breast conservation was applied in between 3 cycles of CMF or after completion of 6 cycles of CMF or anthracyclin containing regimens when Hb already has been restored to normal levels. Therefore, the evaluated Hb levels could not impair effectiveness of

Table II. Univariate and multivariate analysis for nadir Hb with regard to overall survival.

	Univariate			Multivariate		
	HR	95% CI	p-value	HR	95% CI	p-value
Tumour size	2.36	1.03–5.40	0.042	3.20	1.17–8.77	0.023
Haemoglobin	1.59	1.13–2.22	0.008	1.53	1.03–2.32	0.037
Nodal-status	1.69	0.71–4.00	0.232	2.37	0.85–6.62	0.100
Grading	1.89	0.84–4.25	0.122	1.36	0.50–3.67	0.537
ER	0.40	0.18–0.87	0.022	0.43	0.10–1.72	0.235
PR	0.40	0.18–0.88	0.023	0.63	0.14–2.89	0.560
Type of surgery	0.478	0.22–1.03	0.061	0.72	0.25–2.05	0.541
Type of CTX	1.16	0.50–2.73	0.718	1.57	0.55–4.47	0.392
Dose intensity	0.99	0.96–1.02	0.749	0.98	0.96–1.02	0.517
Age	1.01	0.98–1.05	0.365	0.99	0.95–1.03	0.615

Table III. Multivariate analysis for nadir Hb with regard to disease-free and distant disease-free survival.

	DFS			DDFS		
	HR	95% CI	p-value	HR	95% CI	p-value
Tumour size	2.94	1.26–6.84	0.012	2.94	1.13–7.63	0.026
Haemoglobin	1.25	0.87–1.79	0.237	1.54	1.04–2.32	0.033
Nodal-status	3.22	1.27–8.10	0.013	2.40	0.89–6.45	0.083
Grading	1.00	0.43–2.33	0.987	1.11	0.42–2.89	0.825
ER	0.51	0.17–1.53	0.235	0.50	0.13–1.80	0.293
PR	0.49	0.14–1.63	0.247	0.56	0.13–2.32	0.430
Type of surgery	1.05	0.42–2.64	0.910	0.86	0.31–2.39	0.778
Type of CTX	1.65	0.67–4.07	0.270	1.42	0.51–3.94	0.500
Dose intensity	0.97	0.94–1.00	0.122	1.00	0.96–1.04	0.816
Age	0.96	0.93–1.00	0.065	0.98	0.94–1.01	0.320

radiotherapy and subsequent local relapse and DFS. The severity of the myelosuppression has an impact on dose intensity of chemotherapy delivered. We were aware of this possible bias and therefore the cytotoxic regimen used and the dose intensity of cytotoxic therapy was included in the analyses. Nevertheless, the results were confirmed in the multivariate model.

The microenvironment of solid tumours is hypoxic compared with normal tissue [9]. A direct association between anaemia and intratumoural hypoxia in breast cancer has been demonstrated recently [10]. There is increasing evidence that hypoxia can impair drug delivery in solid tumours [11,12]. As a result of decreasing oxygen diffusion in tumours the fraction of proliferating cells decreases. An increasing number of reports have demonstrated radiation therapy and cytotoxic treatment, which are active against rapidly dividing cells, to be more effective in well-oxygenated conditions [13,14]. Initial clinical data showed breast tumours of patients with low Hb levels to have an impaired response to neoadjuvant chemotherapy [6]. In contrast, our study population represents patients in the adjuvant setting without macroscopic residual disease. Nevertheless, with the increasing understanding of the role of neoangiogenesis [15] in malignant tumour growth it is evident that hypoxia already occurs in tumours of less than a millimetre [16]. Furthermore, data from animal trials suggest that improving the oxygenation is more effective in small neoplasms rather than in large tumours [14]. Therefore, in theory, hypoxia may not only be a factor for treating advanced disease but may already be very important in any step of treating solid malignancies including the adjuvant treatment of occult micrometastases. However, there is currently no exact explanation for the observed phenomenon and the detailed mechanism still needs further elucidation.

The incidence of anaemia (Hb <10 g/dl) in patients with advanced breast cancer who received anthracyclin-containing regimes [17] is reported to be in a range from 4% to 25%. Although anaemia is thought to be rare in patients with primary breast cancer, a recent report demonstrated clinically significant anaemia to be present in 18% of non-metastatic breast cancer patients receiving adjuvant chemotherapy [18]. There are various approaches to improve tumour oxygenation: one is to increase the number of red blood cells and therefore the amount of haemoglobin available to transport oxygen. Little attention has been paid to raising haemoglobin levels except in patients with grade 3 and 4 anaemia. However, early correction of moderate anaemia would have the potential to modify the hypoxic environment of solid tumours. An increase of haemoglobin by 20% produces a theoretical decrease in hypoxic tissue volume of approximately 30% [19]. Clinical trials have demonstrated the ability of recombinant human erythropoietin to increase haemoglobin levels and improve quality of life in patients with metastatic breast cancer [20]. Furthermore, promising initial results for the use of epoetin alfa, regarding improved outcome for breast cancer patients receiving chemotherapy, have been reported. Larsson et al. [21] reported enhanced tumour response rates in patients who suffered from advanced breast cancer and who had received erythropoietin. In addition, the trial conducted by Littlewood et al. [22] found a non- significant trend for improved survival in patients receiving epoetin alfa. However, the discordant results of the clinical trial reported by Leyland-Jones [23] raised serious concerns about the risk of increased tumour cell proliferation during erythropoietin treatment. This multi-centre randomized, double-blind, placebo-controlled trial investigating the effect of rhEPO as an adjunct to chemotherapy on the survival of advanced breast cancer was terminated prematurely because a higher mortality rate in the erythropoietin group was observed. Although the results of this report must be taken seriously, the authors them-

selves voiced concerns that the imbalance of risk factors between the treatment groups could have adversely affected the interpretation of these findings. One explanation could be that on a molecular level the presence of erythropoietin receptors on tumour cells is thought to promote survival of tumour cells as well as tumour growth [24,25]. However, the function and expression pattern of erythropoietin receptors as well as the interaction with anaemia-induced hypoxia on angiogenesis and early tumour cell growth needs further investigation.

In summary, low Hb levels during adjuvant chemotherapy may negatively influence survival of patients with primary breast cancer requiring systemic cytotoxic therapy. We are aware of the retrospective nature and the small sample size of the underlying study and the results have to be interpreted with great caution. Therefore, the underlying study must be considered to be hypothesis-generating. Despite the controversy concerning the safety of erythropoietin in patients with advanced breast cancer, other investigators should not be discouraged from further exploring erythropoietin as an adjuvant cancer treatment. Further prospective randomized trials are warranted to examine the value of correcting anaemia with regard to an increase in chemosensitivity in women with breast cancer.

References

[1] Skillings JR, Sridhar FG, Wong C, Paddock L. The frequency of red cell transfusion for anemia in patients receiving chemotherapy. Am J Clin Oncol 1993;16:22–5.

[2] Bush RS, Jenkin RD, Alt WE, Beale FA, Bean H, Dernbo AJ, et al. Definitive evidence for hypoxic cells influencing cure in cancer therapy. Br J Cancer 1978;37:302–6.

[3] Bush RS. The significance of anemia in clinical radiation therapy. Int J Radiot Oncol Biol Phys 1986;12:2047–50.

[4] Hong JH, Chen MS, Lin FJ, Tang SG. Prognostic assessment of tumor regression after external irradiation for cervical cancer. Int J Radiat Oncol Biol Phys 1992;222: 913–7.

[5] Obermair A, Handisurya A, Kaider A, Sevelda P, Kölbl H, Gitsch G. The relationship of pre-treatment serum haemoglobin level to the survival of epithelial ovarian carcinoma patients. Cancer 1998;83:726–31.

[6] 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.

[7] Obermair A, Cheuk R, Horwood K, et al. Impact of haemoglobin levels before and during concurrent chemoradiotherapy on the response of treatment in patients with cervical carcinoma. Cancer 2001;92:903–7.

[8] Grogan M, Thomas GM, Melamed I, et al. The importance of haemoglobin levels during radiotherapy for carcinoma of the cervix. Cancer 1999;86:1528–36.

[9] Höckel M, Vorndran B, Schlenger K, Baussmann E, Knapstein PG. Tumor oxygenation: a new predictive parameter in locally advanced cancer of the uterine cervix. Gynecol Oncol 1993;51:141–9.

[10] Vaupel P, Mayer A, Briest S, Höckel M. Oxygenation gain factor: a novel parameter characterizing the association between haemoglobin level and oxygenation status of breast cancers. Cancer Res 2003;63:7634–7.

[11] Simpson-Herren L, Noker PE. Diversity of penetration of anti-cancer agents into solid tumours. Cell Prolif 1991;24: 355–65.

[12] Teicher BA. Physiologic mechanisms of therapeutic resistance: blood flow and hypoxia. Hematol Oncol Clin North Am 1995;9:475–506.

[13] Brown JM. Tumor hypoxia, drug resistance and metastases. J Natl Cancer Inst 1990;82:338–45.

[14] Rockwell S. Oxygen delivery: implications for the biology and therapy of solid tumors. Oncol Res 1997;9:383–90.

[15] Shweiki D, Itin A, Soffer D, Keshet E. Vascular endothelial growth factor induced by hypoxia may mediate hypoxia-initiated angiogenesis. Nature 1992;359:843–5.

[16] Moulder JE, Rockwell S. Tumor hypoxia: its impact on cancer therapy. Cancer Metastasis Rev 1987;5:313–41.

[17] Ardizzoni A, Venturini M, Sertoli MR, et al. Granulocyte-macrophage colony-stimulating factor (GM-CSF) allows acceleration and dose intensity increase of CEF chemotherapy: a randomised study in patients with advanced breast cancer. Br J Cancer 1994;69:385–91.

[18] 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.

[19] Degner FL, Sutherland RM. Mathematical modelling of oxygen supply and oxygenation in tumor tissues: prognostic, therapeutic and experimental implications. Int J Radiat Oncol Biol Phys 1988;15:391–7.

[20] Olsson AM, Svensson JH, Sundström J, et al. Erythropoietin treatment in metastatic breast cancer:effects on Hb, quality of life and need for transfusion. Acta Oncol 2002;41:517–24.

[21] Larsson AM, Landberg G, Pahlman S, Albertsson M. Erythropoietin enhances response to treatment in patients with advanced breast cancer. Acta Oncol 2004;43:594–7.

[22] Littlewood TJ, Bajetta E, Nortier JWR, Vercammen E, 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 2001;11: 2865–74.

[23] Leyland-Jones B. Breast cancer trial with erythropoietin terminated unexpectedly. Lancet Oncol 2003;4:459–60.

[24] Acs G, Acs P, Beckwith SM, et al. Erythropoietin and erythropoietin receptor expression in human cancer. Cancer Res 2001;61:3561–5.

[25] Yasuda Y, Fujita Y, Matsuo T, et al. Erythropoietin regulates tumour growth of human malignancies. Carcinogenesis 2003;24:1021–9.