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Original Research Report

Pretreatment serum hemoglobin level as a predictive factor of response to neoadjuvant chemotherapy in patients with locally advanced squamous cervical carcinoma: A preliminary report

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Abstract

Objective. The aim of this study was to evaluate the predictive value of pretreatment serum hemoglobin level (Hb) together with a series of clinical and pathological variables available before neoadjuvant chemotherapy in locally advanced squamous cervical cancer.

Methods. The influence on response to neoadjuvant chemotherapy of a series of pretreatment clinico-pathological features: hemoglobin level at diagnosis, age, parity, menopausal status, body mass index, clinical stage, tumor diameter, and nuclear grading were analyzed on 73 patients with locally advanced cervical cancer treated with platinum-based neoadjuvant chemotherapy followed by radical surgery. The relationships between pretreatment variables and response to chemotherapy were assessed in univariate and multivariate settings. A univariate and multivariate logistic regression model was adapted to predict an "optimal" response (pathological complete response or more than 50% reduction in tumoral diameter) or "sub-optimal" response (<50% reduction in tumoral diameter).

Results. Seventy-three patients—clinical stage: Ib2: 29 (39.7%) IIa: 22 (30.1%) IIb: 22 (30.1%)—received 3 cycles of platinum-based neoadjuvant chemotherapy followed by type III radical hysterectomy. A complete response to neoadjuvant chemotherapy was significantly associated with higher level of pretreatment hemoglobin (mean 14.0 mg/dl) compared to patients with ≥50% response (12.7 mg/dl) or <50% (11.9 mg/dl) ($P = 0.002$). At multivariate analysis, Hb level was found to be the most powerful and significantly related factor to response to neoadjuvant chemotherapy. A hemoglobin threshold of 12 mg/dl was able to distinguish between patients—with ≥12 mg/dl—at higher probability to respond to neoadjuvant chemotherapy from the ones at lower probability (hemoglobin level under 12 mg/dl). Patients with a complete response to chemotherapy had a 100% survival compared to 93.1% and 53.8% for patients with responses ≥50% and <50% respectively ($P = 0.0001$). Patients with a pretreatment hemoglobin level of ≥12 mg/dl showed a survival of 87% compared to 63% for patients with a lower hemoglobin level ($P = 0.008$).

Conclusions. Pretreatment Hb level showed a prognostic and independent predictive value for response to neoadjuvant chemotherapy in locally advanced cervical cancer. In our preliminary report, performed on a limited sample, a threshold of 12 mg/dl seems to be helpful to distinguish between "optimal" and "non-optimal" response.
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Keywords: Hemoglobin; Response to chemotherapy; Locally advanced squamous cervical cancer

Introduction

Cervical cancer is the third most common gynecological malignancy in the developed world. Locally advanced disease often shows a 5-year overall survival of <70% [1]. Multimodal treatment strategies, including concomitant

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Table 1
Univariate analysis for response to chemotherapy

Clinical parameter	CR	≥50%	<50%	*P* value
Age (mean)	47.7	52.1	47.4	0.30[a]
Parity (mean (mean rank))	3.0 (46.4)	2.1 (36.2)	1.8 (31.4)	0.05[b]
Menopausal status (%)	29.4	44.1	26.5	0.30[c]
BMI (mean)	25.5	24.4	24.6	0.57[a]
Stage (%)				0.86[c]
Ib[2]	9 (31.0)	10 (34.5)	10 (34.5)	
IIa	5 (22.7)	9 (40.9)	8 (36.4)	
IIb	4 (22.2)	10 (34.5)	9 (30.8)	
Grading (%)				0.27[c]
1	–	1 (3.4)	–	
2	7 (38.9)	7 (24.1)	13 (50.0)	
3	11 (61.1)	21 (72.4)	13 (50.0)	
Tumor diameter—cm (mean)	56.6	52.9	53.4	0.57[a]
Hb pretreatment level—mg/dl (mean)	13.8	12.7	11.9	0.002[a]

CR: complete response; ≥50%: reduction of tumoral diameter of 50% or more after NACT; <50%: reduction of tumoral diameter of <50% after NACT. Underscored: statistical significant at 0.05 level (2-sided).
[a] *F* test (ANOVA).
[b] *U* test (Kruskal–Wallis test).
[c] Pearson's Chi-square test.

cisplatin-based chemotherapy and radiotherapy or neoadjuvant chemotherapy followed by radical surgery or by a combination of concurrent chemoradiation and surgery had been claimed to improve survival and local control rates [2]. Neoadjuvant chemotherapy (NACT) followed by radical surgery (RS) has received increasing attention, being demonstrated to be feasible, and the outcome has been improved. In particular, the operability rate rose from 48% to 100% after NACT with no influence on surgery-related morbidity. The observed 5-year survival rate in patients treated with NACT followed by surgery was higher than in an exclusive radiation therapy group by 65% versus 46% [3–5]. Some efforts have sought to predict chemotherapy resistance by assessing biochemical factors related to tumor cell biology and tumor aggressiveness [6–8]. The respective merits of these treatments will be clarified when the results of new ongoing randomized controlled trials will be available.

Anemia is the most frequently observed hematological abnormality factor among cancer patients; however, its impact on tumor biology is not well understood. Several recent retrospective clinical studies showed that anemia is not only a negative prognostic factor, impairing disease-free and overall survival, but also a negative predictive parameter in radiotherapy-treated patients with solid tumors, including carcinoma of the cervix [9]. Many reports have documented a correlation between Hb levels before and during treatment and the response to chemotherapy [10], suggesting low Hb level as a negative predictive parameter in chemotherapy-treated patients affected by several solid tumors. It is postulated that lower Hb levels resulting in decreased oxygen carrying capacity may lead to increased tumor hypoxia, chemotherapy resistance, and increased tumor angiogenesis [11].

The aim of this report is to investigate whether a relationship exists between pretreatment Hb levels and response to neoadjuvant chemotherapy in patients treated with NACT and radical surgery. Other pretreatment clinical variables, possibly predictive of chemotherapy response, are investigated.

Methods

Seventy-three patients with locally advanced cervical cancer, staged Ib2–IIb, underwent neoadjuvant chemotherapy followed by radical surgery at the Gynecology Oncology department of the University of Turin between 1997 and 2004 (see Table 1). Data were collected in a database and entered with the following fields: FIGO stage Ib2–IIb disease, histologically confirmed squamous cervical cancer, no previous radiation, treatment with neoadjuvant chemotherapy followed by radical surgery (type III radical hysterectomy and pelvic and paraortic lymphadenectomy), availability of the following pretreatment variables: hemoglobin level at diagnosis, age, parity, menopausal status, body mass index, clinical FIGO stage, tumor diameter, nuclear grading on tumor biopsies, response to chemotherapy according to RECIST criteria for solid tumors, and follow-up data. The response to chemotherapy was reclassified as complete response (disappearance of all microscopic neoplastic foci with negative lymph nodes), tumor load reduction of more than 50% (reduction of the maximum tumoral diameter of more than 50% compared to the initial measurement), tumor load reduction of <50% (reduction of the maximum tumoral diameter of <50% compared to the initial measurement). Patients were all

Table 2
Univariate logistic analysis for "non-optimal" response to chemotherapy (<50% reduction)

Clinical pretreatment parameter	HR	CI 95%[a]	*P* value
Age	0.98	0.94–1.05	0.21
Parity	0.71	0.48–1.05	0.09
Menop status	2.14	0.79–5.77	0.13
BMI	0.98	0.85–1.12	0.78
Stage			0.98
Ib2	1		
IIa	1.08	0.34–3.45	
IIb	1.08	0.34–3.45	
Grading (%)			0.25
1	1		
2	0.05	0.00–2.85	
3	2.28	0.84–6.16	
Tumor diameter (cm)	0.99	0.95–1.03	0.76
Hb pretreatment level mg/dl (continuous)	0.66	0.49–0.90	0.008
Hb ≥ 12 mg/dl	1		
Hb < 12 mg/dl	6.83	2.16–21.60	0.001

HR: hazard ratio.
[a] CI: 95% confidence interval.

Table 3
Multivariate logistic analysis for "non-optimal" response to chemotherapy

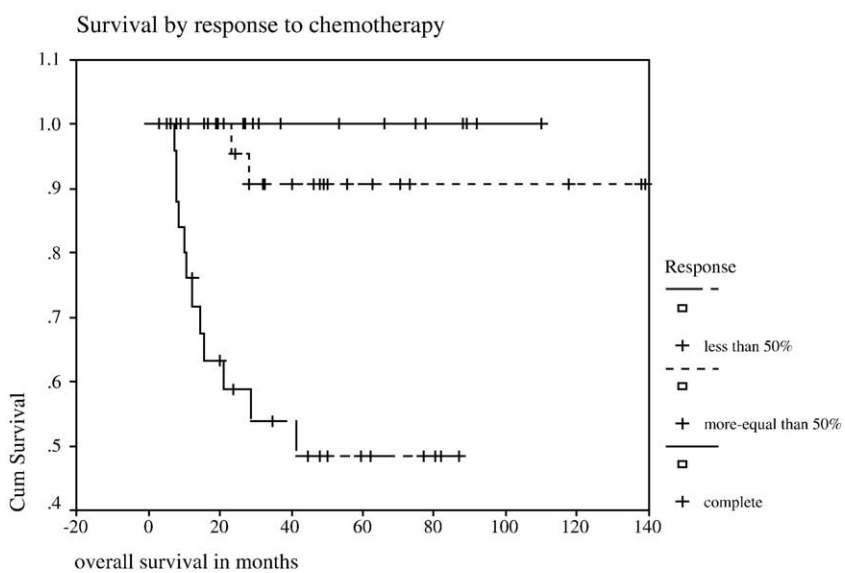
Variables in the equation	HR	CI 95%[a]	Wald	−2 log likelihood	*P* value
Hb pretreatment level mg/dl (continuous)	0.66	0.49–0.90	6.88	87.2	0.008
Hb ≥ 12 mg/dl	1		10.70	83.3	
Hb < 12 mg/dl	6.83	2.16–21.60			0.001

HR: hazard ratio.
[a] CI: 95% confidence interval.

treated with a platinum-based chemotherapy giving at least a dose intensity of 20 mg/m^2/weekly for 3 courses every 21 days. The study protocol had been reviewed by the ethics committee, and written informed consent was obtained from each patient. The relationships between the pretreatment variables and response to chemotherapy were assessed in a univariate setting by means of analysis of variance (ANOVA) for continuous variables and Mann–Whitney non-parametric test to evaluate whether two independent samples are from the same population. A univariate and multivariate logistic regression model is adapted to predict an optimal response (complete or more than 50% reduction) or a suboptimal response (<50% reduction) based on values of a set of pretreatment predictor variables. The Kaplan–Meier model, based on estimating conditional probabilities at each time point when an event occurs, is used to estimate the survival rate of patients with a good and poor response to chemotherapy. Actuarial survival curves are generated, and the log rank test is adapted for comparing the equality of survival distributions. Calculations were executed with the SPSS statistical package version 12 (SPSS Inc, IL, USA).

Results

Seventy-three patients received neoadjuvant chemotherapy. The distribution of clinical stage was as follows: stage Ib2: 29 (39.7%), IIa: 22 (30.1%), IIb: 22 (30.1%). Overall mean age was 49.3 years, and median parity number was 2. Thirty-four patients (46.6%) were menopausal when entering the study. The mean body mass index (BMI) was 24.3 kg/m^2. The grade of differentiation at diagnostic biopsies was as follows: G1 = 1 patient (1.4%), G2 = 27 patients (37.0%), G3 = 45 patients (61.6%). Tumor diameter at diagnostic procedure had an overall median value of 50 cm; 17 patients (23.3%) had a neoplasm less than 5 cm and 56 patients ≥5 cm (76.7%). The response to chemotherapy was complete in 18 (24.7%) patients, ≥50% in 29 (39.7%), and <50% in 26 (35.6%) patients.



Survival Analysis for response to chemotherapy

	Total	Number Events	Number Censored	Percent Censored
Complete response	18	0	18	100.00
More/equal 50% response	29	2	27	93.10
Less than 50% response	26	12	14	53.85
Overall	73	14	59	80.82

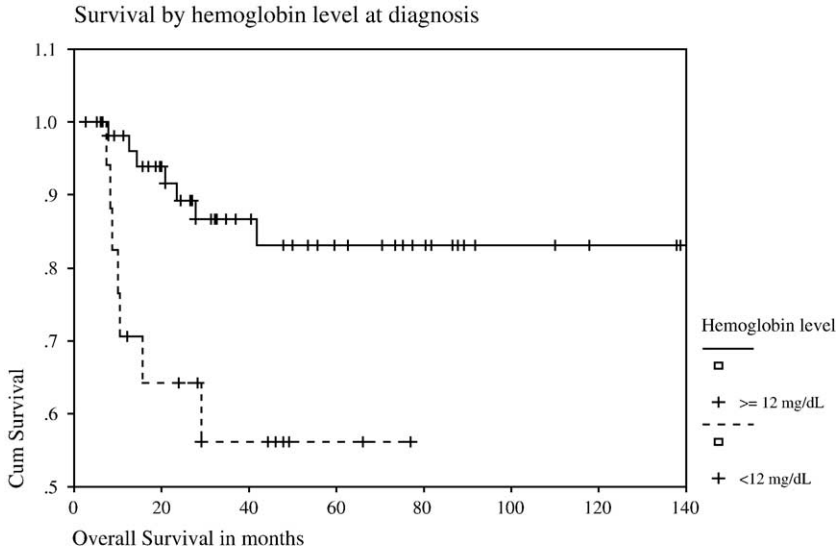
Log Rank =Statistic:19.47 p=0.0001

Fig. 1. Survival curves and analysis for this patient group to stratified by response to chemotherapy.

Table 1 shows a univariate analysis for response to chemotherapy in which the distribution of each predictive factor is observed across the three levels of response: complete, ≥50%, <50%. Patients who demonstrated a complete response had a significantly higher level of pretreatment hemoglobin (13.8 mg/dl) compared to patients with a ≥50% response (12.7 mg/dl) or <50% (11.9 mg/dl; $P = 0.002$). A trend towards a better response is also noticed for patients with a higher parity ($P = 0.05$). Table 2 reports a logistic model created to derive the hazard ratio for a non-optimal response, considered when a <50% reduction in tumor measurement was encountered. The dichotomous dependent variable had the following distribution: 64.4% (47/73 patients) showed complete response or ≥50%, 35.6% showed <50% response (26/73 patients). For each explanatory pretreatment variable, the hazard ratio of <50% response and 95% confidence interval are displayed. At multivariate analysis (Table 3), Hb level is the most powerful and significantly related factor to response to chemotherapy. A patient with an Hb level increment of 1 mg/dl had her risk of not responding to platinum-based chemotherapy decreased at 0.6. On the other hand, a hemoglobin threshold of 12 mg/dl allowed a distinction between two groups where the one with a pretreatment hemoglobin level of ≥12 mg/dl has a probability to respond to neoadjuvant chemotherapy of nearly seven times higher. Fig. 1 shows the Kaplan–Meier actuarial survival curves by response to chemotherapy. Patients with a complete response to chemotherapy had a 100% survival rate compared to 93.1% for ≥50% responders and 53.8% for <50% responders ($P = 0.0001$). Fig. 2 shows the Kaplan–Meier actuarial survival curves for hemoglobin threshold of 12 mg/dl. Patients with a pretreatment hemoglobin level of ≥12 mg/dl showed a survival rate of 87% compared to 63% of patients with a lower hemoglobin level ($P = 0.008$).

Discussion

Neoadjuvant chemotherapy followed by radical surgery emerged as an alternative treatment to conventional radiotherapy (external beam therapy and brachytherapy) and more recently chemoradiotherapy for locally advanced cervical cancer. Awaiting results from ongoing trials, some efforts were made to predict in advance the response to chemotherapy of a subgroup of patients sensitive to the existing drugs to improve survival. There is increasing evidence that the response to chemotherapy is a good, or perhaps the most powerful, prognostic factor in locally advanced cervical cancer. In our report, patients who had a complete response to chemotherapy demonstrated a survival of 100% compared to 93.1% and 53.5% for reduction



Survival Analysis for level of hemoglobin at diagnosis

	Total	Number Events	Number Censored	Percent Censored
HB<12mg/dL	19	7	12	63.16
HB≥12mg/dL	54	7	47	87.04
Overall	73	14	59	80.82

Log Rank : Statistic: 6.92 p=0.0085

Fig. 2. Survival curves and analysis for this patient group stratified by hemoglobin level.

of the tumor of ≥50% and <50%, respectively (log rank: P value = 0.0001). Lacking reliable clinical predictive factors, some authors tested chemotherapy resistance by assessing biochemical factors such as serum levels of squamous cell carcinoma antigen [12], microvessel density [6,7], oncogenes and tumor suppressor genes [13], and cyclooxygenase-2 [8]. Anemia is the most frequently observed hematological abnormality factor among cancer patients. Its impact on tumor biology is not well understood yet [10,14]. Suppression of erythroid progenitor cells by tumor cytokines (IL-6), changes in iron metabolism, alteration of erythropoietin response, or simply chronic hemorrhage are some of the mechanisms that have been associated with pretreatment tumor-associated anemia [15].

In the present study, we tested clinical pretreatment parameters and serum hemoglobin level to predict chemotherapy resistance. Neoadjuvant chemotherapy response was significantly more likely in patients with high pretreatment Hb values; the threshold of 12 mg/dl is shown to be a good cut-off between "optimal" response (complete and ≥50% response) and "non-optimal" response (<50% reduction in tumor diameter). It has been reported repeatedly that anemia is associated with both decreased local control and overall survival in large numbers of patients affected by cervical cancer that are treated with radiotherapy [16–19]. One hypothesis is that hypoxic cell fraction of the tumor increases as a consequence of anemia and confers to these cellular clones a lowered degree of radiosensitivity [20]. Currently, there are few data available on the correlation between Hb pretreatment levels and response to neoadjuvant chemotherapy. In our report, we demonstrated a relationship between high levels of pretreatment serum hemoglobin and good response to neoadjuvant chemotherapy. Our preliminary data have to be confirmed by wider studies. Recombinant human erythropoietin (rh-EPO) or blood transfusion can be used to increase blood Hb levels before chemotherapy and perhaps during the treatment with the aim of improving tumor oxygenation and convert cells to chemosensitivity. On the contrary, it may be supposed that hemoglobin levels may be useful to identify the more aggressive tumors which, because of chemoresistance, should not be treated with neoadjuvant chemotherapy followed by radical surgery.

Conclusions

Pretreatment serum hemoglobin level was found to be predictive of the response to chemotherapy, and a threshold of 12 mg/dl could be helpful to distinguish between "optimal" and poor response. If these results could be confirmed on a wider sample, clinical trials will need to be performed to determine whether to increase hemoglobin levels lead to improved local control rates and survival.

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