[Frontiers in Bioscience 11, 1585-1590, May 1, 2006]

The prognostic role of pre-chemotherapy hemoglobin level in patients with ovarian cancer

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TABLE OF CONTENTS

1. ABSTRACT

Anemia significantly affects quality of life of cancer patients, but the impact of hemoglobin levels on survival is still unclear. The aim of this retrospective study was to assess the prognostic role of pre-chemotherapy hemoglobin levels in patients with ovarian cancer. Two hundred twenty-two patients were divided in 3 groups based on baseline hemoglobin levels (< 10 gr/dl (54 pts., 24%); 10-11.9 gr/dl (87 pts., 39%); ≥ 12 gr/dl (82 pts., 37%)). Correlations among baseline characteristics (age, ECOG performance status, stage, grading, histology, residual disease after primary surgery) and baseline hemoglobin level were analyzed. Poor performance status ($p = 0.03$), more advanced stage ($p = 0.01$), and sub-optimal residual disease ($p = 0.002$) were more frequent in patients with lower hemoglobin values. There was no significant correlation between baseline hemoglobin level and response rate to subsequent chemotherapy. Based on univariate analysis, hemoglobin categories were statistically significant predictors for time to progression ($p = 0.0002$) and overall survival ($p < 0.0001$). Based on multivariate analysis, patients with hemoglobin between 10 and 12 g/dl had a 1.45 hazard ratio (HR) for recurrence and a 1.35 HR of death compared with patients with normal hemoglobin. Patients with hemoglobin < 10 g/dl had a 2.02 HR of recurrence and a 2.49 HR of death compared with patients with normal hemoglobin. These findings show that hemoglobin level prior to chemotherapy is an independent predictor of progression-free survival and overall survival in patients treated for ovarian carcinoma.

2.INTRODUCTION

Anemia is a common finding in cancer patients (1). Gynecological cancers are among the tumors characterized by a higher prevalence of anemia at diagnosis (1). The etiology of cancer-related anemia is tipically multifactorial, potentially including anemia of chronic disease, bone marrow involvement, blood loss, and nutritional deficiencies (2). In ovarian cancer, hemoglobin value of patients candidate to first-line chemotherapy is affected also by the amount of blood lost during the previous debulking surgery.

Impact of anemia on health-related quality of life of cancer patients has been demonstrated by randomized trials and large community based studies (3,4). On the contrary, despite a number of studies addressing the topic, the relationship between hemoglobin levels and survival remains unclear. A systematic review dedicated to this topic showed a correlation between presence of anemia and shorter survival in several tumors (5). In that review, data regarding ovarian carcinoma were derived from only two published studies (6, 7) and were not conclusive. Recently, some other studies have been published, suggesting a prognostic role of anemia in ovarian cancer patients (8, 9).

Objectives of this retrospective analysis were to describe the prevalence of anaemia in patients candidated to first-line chemotherapy for epithelial ovarian carcinoma, to evaluate the correlation among pre-chemotherapy hemoglobin level and patients'characteristics (age,

performance status), to evaluate the correlation among pre-chemotherapy hemoglobin level and tumor characteristics (stage, grading, histology, residual disease after surgery) and to evaluate the prognostic impact of baseline anemia on the outcome of the patients (objective response to chemotherapy, progression-free survival, overall survival).

3. PATIENTS AND METHODS

The present analysis has been conducted on the data of the patients receiving first-line chemotherapy for ovarian carcinoma at the Division of Medical Oncology B of the National Cancer Institute of Naples between 1996 and 2002.
In the present analysis, baseline hemoglobin value is defined as the hemoglobin value registered before the start of chemotherapy. Patients have been divided in three categories, corresponding to the grade of anemia according to National Cancer Institute – Common Toxicity Criteria version 2.0 (10). The three categories were: (a) patients with normal baseline hemoglobin value (≥ 12 gr/dl); (b) patients with mild anemia (baseline hemoglobin value ≥10 and < 12 gr/dl); (c) patients with moderate to severe anemia (baseline hemoglobin value < 10 gr/dl).

3.1 Statistical methods

Correlations among main patient or tumor characteristics (ECOG performance status, stage, grading, histology, residual disease after primary surgery) and baseline hemoglobin level were described by contingency tables and analyzed by chi square test. Age distribution in the three hemoglobin categories was analyzed by the Kruskal-Wallis test.

Objective response to first-line chemotherapy was grouped in two categories: yes (complete response or partial response) and no (stable disease, progressive disease or not evaluated). Impact of baseline hemoglobin level categories on objective response rate to chemotherapy was analyzed by chi square test.

Progression-free survival (PFS) was defined as the interval from date of baseline visit to date of progression or death whichever occurred first or last follow-up information for patients alive and progression-free. Overall survival (OAS) was defined as the interval from date of baseline visit to date of death or last follow-up information for alive patients. In order to analyze the impact of baseline hemoglobin level on PFS and OAS, survival curves were drawn with the Kaplan-Meier product limit method (11) and compared with the Mantel-Haenszel test (12). Relative hazard of progression and death with 95% confidence intervals (CI) were estimated by using the Cox proportional hazards model (13), considering age (increasing), performance status (1 vs 0 and 2 vs 0), stage of disease (increasing), residual disease after primary surgery (absent or < 1 cm > 1 cm) as covariates.

All statistical tests were two-tailed and P values less than 0.05 were considered statistically significant. Analyses were performed with S-PLUS software (S-PLUS 6.0 Professional, release 1; Insightful Corporation, Seattle, WA, USA).

4 RESULTS

4.1 Patients

Between 1996 and 2002, 225 patients received first-line chemotherapy for epithelial ovarian carcinoma. Baseline hemoglobin value was not recorded for 3 patients, that have been excluded from the present analysis. Main characteristics of the 222 patients analyzed are summarized in table 1. The median age of the patients was 57 years (range 22-84). Most of the patients, at the baseline evaluation before starting chemotherapy, had a good Performance Status (0 or 1 in 88% of the patients). Stage of the disease was advanced in the majority of the patients (59% stage III, 27% stage IV). Two thirds of the patients started chemotherapy with a sub-optimal debulking surgery (residual disease larger than 1 cm).

Eighty-two patients (37%) had a normal baseline hemoglobin value (>12 gr/dl), whilst the remaining 140 patients (63%) showed some degree of anemia: anemia was mild in 87 patients (39%) and moderate in 53 patients (24%).

4.2 Association of hemoglobin levels with patients'characteristics

Correlation among anemia and main baseline characteristics of the patients are detailed in table 2. There was a correlation between baseline hemoglobin value and ECOG performance status: patients with PS 0 were 59%, 49% and 34% in the group with normal hemoglobin value, mild and moderate anemia, respectively. Patients with PS 2, on the contrary, were 6%, 13% and 21% in the three groups, respectively. This correlation was statistically significant (p=0.03). Age of the patients was similar in the three hemoglobin categories.

As for correlation between baseline hemoglobin value and main tumor characteristics, there was a statistically significant correlation with advanced stage of disease (p=0.01). Hemoglobin values were significantly lower in patients with residual disease than in those with no detectable residual tumor after initial surgery (p=0.002).

4.3 Association of hemoglobin levels with treatment outcomes

Correlation among anemia and outcomes of the patients (response to chemotherapy, progression-free survival and overall survival) are described in table 3. All patients received a platinum-based combination chemotherapy. Baseline hemoglobin value did not significantly affect the proportion of patients with objective response to chemotherapy: a complete or partial response was documented in 62%, 67% and 60% for patients with normal hemoglobin value, with mild and moderate anemia, respectively (p=0.72).

Actuarial progression-free survival curves scattered by baseline hemoglobin category are shown in Figure 1. Median progression-free survival was 19.7

Table 1. Baseline characteristics of the 222 patients

	Overall (n=222)
Age (years)	
Median	57
Range	22-84
PS	
0	109 (49%)
1	86 (39%)
2	27 (12%)
Stage	
I	18 (8%)
II	15 (7%)
III	130 (59%)
IV	59 (27%)
Grading	
G1	10 (5%)
G2	85 (38%)
G3	127 (57%)
Histology	
Serous	86 (39%)
Papillary	38 (17%)
Endometrioid	31 (14%)
Mucinous	19 (9%)
Other	48 (21%)
Residual disease	
Absent or <1 cm	75 (34%)
> 1 cm	147 (66%)

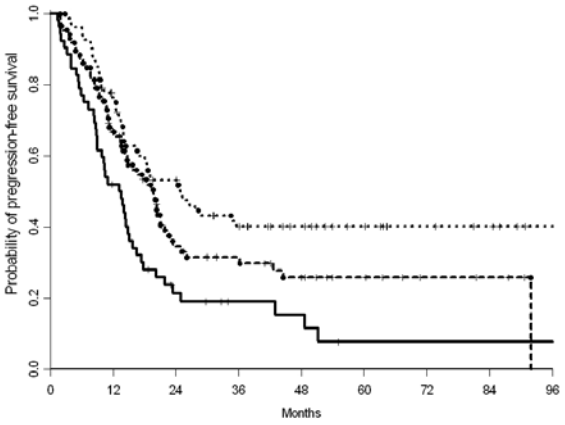

Figure 1. Kaplan-Meyer curves of progression-free survival of patients with epithelial ovarian carcinoma according to pre-chemotherapy hemoglobin value. Crosses represent censoring.

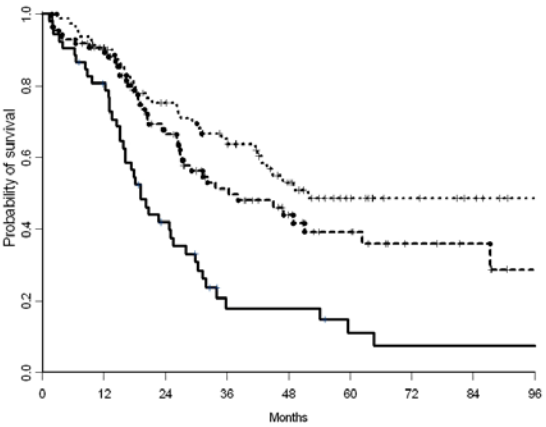

Figure 2. Kaplan-Meyer curves of overall survival of patients with epithelial ovarian carcinoma according to pre-chemotherapy hemoglobin value. Crosses represent censoring.

months and 13.2 months for patients with mild and moderate anemia, respectively, and 24.9 months for those with normal baseline hemoglobin values (p=0.0002 at Log-Rank test). Multivariable analysis (table 4), including baseline hemoglobin, age, performance status, stage, and residual disease after surgery as covariates, showed that anemia had a prognostic role, with hazard ratios of death equal to 1.45 (95% CI 0.97-2.17) and 2.02 (95% CI 1.31-3.12) for patients with mild and moderate anemia, respectively. Also stage of disease showed an independent prognostic role.

Actuarial overall survival curves scattered by baseline hemoglobin category are shown in Figure 2. Median overall was 36.3 months and 19.2 months for patients with mild and moderate anemia, respectively, and 51.8 months for those with normal baseline hemoglobin values (p<0.0001 at Log-Rank test). Multivariable analysis (table 5), including baseline hemoglobin, age, performance status, stage, and residual disease after surgery as covariates, showed that anemia had a prognostic role, with hazard ratios of death equal to 1.35 (95% CI 0.86-2.13) and 2.49 (95% CI 1.55-3.99) for patients with mild and moderate anemia, respectively. Also stage of disease and worse performance status showd an independent prognostic role.

5. DISCUSSION

Our data show a high prevalence of anemia in patients candidated to first-line chemotherapy for ovarian cancer. The significant impact of anemia on quality of life of cancer patients is well documented: presence of anemia has potential consequences in terms of fatigue, exhaustion, weakness, headache, decreased activity and impairment of several functional domains of health-related quality of life (14). In our data, this aspect is underlined by a clear corrleation between presence of anemia and worse performance status. This represent an important clinical problem, that may also become more serious during subsequent chemotherapy, due to mielotoxicity of cytotoxic drugs. Furthermore, baseline hemoglobin values have been shown predictive of the need for blood transfusions during subsequent platin-based chemotherapy for ovarian cancer (15).

The most intriguing aspect of our results is the clear prognostic role showed by pre-chemotherapy hemoglobin value on patients'outcome, both in terms of progression-free survival and in terms of overall survival. Our data are consistent with other results suggesting the same correlation in ovarian cancer (7,8,9) and in other solid tumors (5). Although anemia was correlated with prognostic factors related to tumor burden (advanced stage and suboptimal residual disease after primary surgery), at multivariable analysis low baseline hemoglobin values remained an independent prognostic factor for progression-free and overall survival. Interestingly, in our series residual disease after primary surgery showed no prognostic role, and this might be at least partially explained by the effect of interval debulking surgery (16). Infact, interval surgery was regularly performed at our

Table 2. Correlation between baseline hemoglobin value and main baseline characteristics characteristics of the 222 patients

	Hgb < 10 gr/dl (n = 53)	**Hgb 10 – 11.9 gr/dl (n=87)**	**Hgb ≥ 12 gr/dl (n=82)**	**P**
Age (years)				0.24[1]
Median	60	56	55	
Range	40-84	22-83	26-80	
	Number of patients (column percentage)			
PS				0.03[2]
0	18 (34%)	43 (49%)	48 (59%)	
1	24 (45%)	33 (38%)	29 (35%)	
2	11 (21%)	11 (13%)	5 (6%)	
Stage				0.01[2]
I	2 (4%)	4 (5%)	12 (15%)	
II	-	5 (6%)	10 (12%)	
III	35 (66%)	55 (63%)	40 (49%)	
IV	16 (30%)	23 (26%)	20 (24%)	
Grading				0.90[2]
G1	3 (6%)	3 (3%)	4 (5%)	
G2	19 (36%)	32 (37%)	34 (41%)	
G3	31 (58%)	52 (60%)	44 (54%)	
Histology				0.63[2]
Serous	24 (45%)	33 (38%)	29 (35%)	
Papillary	10 (19%)	15 (17%)	13 (16%)	
Endometrioid	7 (13%)	10 (11%)	14 (17%)	
Mucinous	5 (9%)	6 (7%)	8 (10%)	
Other	7 (13%)	23 (27%)	16 (22%)	
Residual disease				0.002[2]
Absent or <1 cm	10 (13%)	26 (35%)	39 (52%)	
> 1 cm	43 (29%)	61 (41%)	43 (29%)	

[1] Kruskal-Wallis test; [2]Chi square test

Table 3. Patients' outcomes by pre-chemotherapy hemoglobin value

	Hgb < 10 gr/dl (n = 53)	**Hgb 10 – 11.9 gr/dl (n=87)**	**Hgb ≥ 12 gr/dl (n=82)**	**p**
Objective response				0.72[1]
Yes	32 (60%)	58 (67%)	51 (62%)	
No	21 (40%)	29 (33%)	31 (38%)	
Time to progression (months)				0.0002[2]
median	13.2	19.7	24.9	
95% CI	9.0 – 15.8	14.7 – 22.8	18.06 - NA	
Overall survival (months)				<0.0001[2]
Median	19.2	36.3	51.8	
95% CI	16.3 – 28.1	27.3 - NA	41.9 - NA	

[1] Chi square test; [2] Mantel-Haenszel test

Table 4. Multivariable analysis of progression-free survival

Covariate	**Hazard Ratio**	**95% CI**	**P**
Age at diagnosis			
Increasing	1.02	1.01 – 1.04	0.004
Performance Status			
1 vs 0	1.22	0.82 – 1.82	0.32
2 vs 0	1.42	0.83 – 2.43	0.20
Stage			
Increasing	1.44	1.07 – 1.94	0.02
Hemoglobin level			
Intermediate vs better	1.45	0.97 – 2.17	0.07
Worse vs better	2.02	1.31 – 3.12	0.001
Residual disease after surgery			
absent or ≤1 cm vs. >1 cm	1.14	0.73 – 1.77	0.57

Institution during those years for patients without optimal primary debulking.

A certain explanation for the prognostic role of anemia is still lacking. A possible reason is that anemia and subsequent reduced tissue oxygenation might decrease tumoral cell sensitivity to cytotoxic treatment. However, while this seems true for sensitivity to radiotherapy (17), relation between oxygenation and response to chemotherapy, although suggested by some pre-clinical evidence (18), is not well defined (19). Furthermore, in our data we did not find any correlation between baseline

Table 5. Multivariable analysis of overall survival

Covariate	Hazard Ratio	95% CI	P
Age at diagnosis			
Increasing	1.01	0.99 – 1.03	0.13
Performance Status			
1 vs 0	1.47	0.96 – 2.26	0.08
2 vs 0	1.88	1.06 – 3.33	0.03
Stage			
Increasing	1.79	1.27 – 2.53	0.0008
Hemoglobin level			
Intermediate vs better	1.35	0.86 – 2.13	0.19
Worse vs better	2.49	1.55 – 3.99	0.0002
Residual disease after surgery			
absent or ≤1 cm vs. >1 cm	1.02	0.63 – 1.65	0.94

anemia and objective response to subsequent platinum-based chemotherapy, so better prognosis for patients with higher hemoglobin levels dose not seem to be mediated by an increase in chemotherapy activity.

An alternative hypothesis to explain the prognostic role of anemia is that decrease in hemoglobin levels is related to a more aggressive tumor phenotype. Tumor cells are known to produce and secrete several soluble molecules (such as tumor necrosis factor, interferon gamma and interleukin-1) that might be able to decrease hemoglobin levels, by hemolysis, suppression of erythropoiesis, and impairment of erythropoietin response of erythroid medullary precursors (2,20). According to this hypothesis, anemia should be regarded as a sort of paraneoplastic syndrome, an epiphenomenon of biologic aggressiveness of cancer. In other words, anemia might not be the direct cause of decreased survival, and this hypothesis is supported by our data showing a significant correlation between lower hemoglobin level and higher tumor burden, in terms of stage and residual disease after primary surgery. However, multivariable analysis revealed that anemia has a prognostic role independent from those variables, and it cannot be reduced to a surrogate for other adverse factors.

From this study it is clear that – as either a direct or indirect cause – patients presenting to chemotherapy with anemia have a lower survival. Given the significant reduction in patient survival caused by lower hemoglobin levels demonstrated in some tumors, an obvious consequence of these results has been to hypothesize that the correction of anemia should determine a improved survival. However, our data, with the absence of relation with objective response and the suggested role of anemia as epiphenomenon of aggressive cancer, does not strongly support this hypothesis.

In conclusion, this study shows that anemia is a strong predictor of worse prognosis in ovarian cancer patients candidate to first-line chemotherapy. Of course, additional, prospective studies are needed to determine whether the correction of anemia may improve prognosis.

6. ACKNOWLEDGEMENTS

This study was partially supported by AIRC (Associazione Italiana per la Ricerca sul Cancro). Massimo Di Maio is recipient of a FIRC (Fondazione Italiana per la Ricerca sul Cancro) fellowship.

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Key Words: Hemoglobin, Ovarian Cancer, Tumor, Neoplasia, Treatment,

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