RESEARCH COMMUNICATION

Prognostic Significance of Hemoglobin Levels in Patients with Primary Epithelial Ovarian Carcinoma Undergoing Platinum-based Chemotherapy

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Abstract

The aim of this study was to evaluate the prognostic impact of hemoglobin (Hb) levels before and throughout the course of platinum-based chemotherapy in patients with primary epithelial ovarian cancer (EOC). Medical records of patients who had undergone initial surgery followed by platinum-based chemotherapy for EOC were retrospectively studied. Univariate and Cox-regression models were used to evaluate the prognostic impact of various factors including Hb levels before and throughout chemotherapy in terms of overall survival. Additionally, sensitivity/specificity were calculated using receiver operating curves (ROCs) and Kaplan-Meier studies were used to determine optimal cut-off levels. The median duration of follow-up was 37.0 months. Degree of anemia before starting chemotherapy was significantly related to overall survival (p = 0.001), but the Hb level throughout chemotherapy demonstrated only a borderline relationship (p = 0.062). Only residual tumor after surgery and degree of anemia before starting chemotherapy proved to be independent prognostic factors (p = 0.013 and 0.015, respectively). With sensitivity/specificity and Kaplan-Meier analyses, a Hb level before starting chemotherapy of less than 10.5 g/dl was related to shorter overall survival (p = 0.002). In conclusion, pre-chemotherapy Hb level has a prognostic impact on overall survival in patients with EOC candidate to first-line platinum-based chemotherapy. However, the significance of decreased Hb levels during chemotherapy needs to be clarified in further prospective studies to determine optimal Hb levels for achieving a favorable outcome.

Keywords: Anemia - ovarian cancer - platinum-based chemotherapy - prognosis

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Introduction

Anemia is the most common hematological complication observed in cancer patients. According to the European Cancer Anemia Survey (ECAS) involving approximately 15,000 patients across 24 European countries, 68% of patients experienced anemia at some time during the 6-month follow-up period, depending upon the type of neoplasia (Ludwig et al., 2004). The etiology of cancer-related anemia is multifactorial, possibly associated with nutritional deficiencies, bleeding from tumor sites, bone marrow infiltration by the tumor, and the myelosuppressive effects of anticancer therapies. In addition, patients with cancer often have anemia of chronic disease, characterized by excessive release of cytokines such as interleukin-1, interferon-gamma, and tumor necrosis factor, which interfere with the production of endogenous erythropoietin and inhibit erythroid bone marrow production (Faquin et al., 1992; Weiss et al., 2005).

Anemia has a detrimental impact on quality of life (QoL). Fatigue is the most debilitating symptom of anemia and is one of the most frequently reported and distressing problems in patients with cancer (Stone et al., 2000; Holzner et al., 2002; Ahlberg et al., 2003). Besides the negative effect on QoL, the presence of anemia itself is associated with shorter survival times for several cancers (Caro et al., 2001; Alici et al., 2006). One of the major reasons for this reduced survival is tumor hypoxia which is related to the reduced oxygen carrying capacity of the blood. Low Hb levels result in decreased oxygen transport capacity which causes decreased tumor oxygenation (Vaupel et al., 2003; Boogaerts et al., 2005). Hypoxia may contribute to the malignant behavior of the disease by providing a selection pressure for tumor cells with higher rates of mutation, which ultimately result in increased cellular growth, decreased cell response to apoptosis signals, and therapy resistance (Young et al., 1988; Graeber et al., 1996; Reynolds et al., 1996; Hockel et al., 2001; Vaupel et al., 2003; Van Belle et al., 2003).

Ovarian cancer is the sixth most common cancer in women worldwide and is the leading cause of death among gynecological malignancies in Western Europe and North America. In Thailand, it is the second most common cancer of the female genital tract after cervical cancer with an annual incidence of 5.6 per 100,000 women, and

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an annual death rate of 2.6 per 100,000 women per year (Parkin et al., 2005). Due to the often asymptomatic nature of the early stages of disease, many cases of ovarian cancer present in advanced stage for which the 5-year survival is around 30% (Memarzadeh et al., 2001). The correlation between presence of anemia and survival of patients with ovarian cancer remains unclear. Only few data are currently available concerning the prognostic relevance of Hb levels before and particularly during chemotherapy for these patients. This study was undertaken to clarify the prognostic impact of Hb levels before and throughout the course of platinum-based chemotherapy in patients with primary epithelial ovarian cancer.

Materials and Methods

This retrospective study was conducted on 122 patients with histologically confirmed epithelial ovarian cancer who underwent primary surgery at the Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, between January 2003 and December 2006. All information was obtained by chart review. Criteria for inclusion in the study were as follows: age < 80 years, no past or present secondary malignancy, no other nonmalignancy-associated anemia (e.g. thalassemia or chronic iron deficiency anemia), and receiving at least 6 cycles of platinum-based chemotherapy. The tumor stage and histological diagnosis of each case were determined according to the criteria of the International Federation of Gynecology and Obstetrics (FIGO) and the histological typing system of the World Health Organization (WHO), respectively. Tumors were graded as well (G1), moderately (G2), or poorly (G3) differentiated.

Baseline Hb level in each patient was determined 24-48 hours before the start of chemotherapy. The mean Hb level throughout chemotherapy was calculated as the average of all Hb levels prior to the corresponding chemotherapy cycle. Patients were divided into 3 groups based on the National Cancer Institute Common Toxicity Criteria (NCI-CTC). The three categories were: patients with normal Hb value (> 12 g/dl); patients with mild anemia (> 10 and < 12 g/dl); patients with moderate to severe anemia (< 10 g/dl). Association between clinicopathological variables (ECOG performance status, stage, histology, grading, residual disease after surgery, ascites, and chemotherapy regimen) and pre-chemotherapy Hb levels were described using Pearson's chi square test (or two-tailed Fisher's exact test when appropriate). Overall survival was determined as time interval between date of baseline visit and date of death or last follow-up information for surviving patients. In order to analyze the impact of Hb level before and throughout chemotherapy on overall survival, survival curves were drawn with Kaplan-Meier product limit method.

Univariate analyses of prognostic significance were used to study the influence of clinicopathological parameters on overall survival. A multivariate analysis based on the Cox proportional hazard model was used to test the relative importance of these variables as predictors of survival times. Additionally, optimal cut-off Hb levels before and throughout chemotherapy were integrated in this model. Sensitivity and specificity of the Hb levels before and throughout chemotherapy were calculated using ROC curve to evaluate the prognostic impact on overall survival. Based on the selected cut-off Hb levels, Kaplan-Meier survival curves for lower and higher Hb level were compared.

A p-value of < 0.05 was taken for statistical significance. Data management and statistics were performed using SPSS software for Windows 13.0. The research project was approved by the ethical committee of the Siriraj Hospital, Mahidol University, and was conducted in accordance with the Declaration of Helsinki.

Results

Patients

Between 2003 and 2006, 122 primary epithelial ovarian cancer patients qualified for inclusion in the study. The mean age of patients at diagnosis was 53.2 years (median 53.0; SD 9.7). Most of the patients, at the baseline evaluation before starting chemotherapy, had a good performance status (0 or 1 in 76% of patients). Stage of the disease was advanced in the majority of the patients (45.9% stage III, 11.5% stage IV). Histologically, 43 (35.2%) patients were serous, 25 (20.5%) clear cell, 22 (18%) endometrioid, 8 (6.6%) mucinous, and 24 (19.7%) others. Tumor grade was G1 in 20 (16.4%) patients, G2 in 27 (22.1%), and G3 in 75 (61.5%). Approximately one half of the patients had residual disease ≤ 1 cm after surgery and seventy patients (57.4%) started combination platinum-base chemotherapy with paclitaxel after initial surgery.

The median duration of follow-up was 37.0 months (range, 3.9-70.2 months) and mean overall survival 55 months (95% confidence interval, 51-60 months). The overall 5-year survival probability was 65%. At the end of the observation period, 58 patients (47.5%) were tumor free, 31 patients (25.4%) were alive with tumor, and 33 patients (27%) had died of their disease.

Association of hemoglobin levels with patients' characteristics

Correlations among degree of anemia and main baseline patients' characteristics are given in Table 1. Overall mean Hb levels before and throughout chemotherapy were 10.7 g/dl (SD 1.3) and 10.4 g/dl (SD 0.9), respectively. After classification, only 22 (18%) and 6 (5%) of the patients had normal Hb level (≥ 12 g/gL) before and throughout chemotherapy, while the remaining 100 (82%) and 116 (95%) patients showed some degree of anemia: mild anemia in 66 (54%) and 77 (63%) patients as well as moderate to severe anemia in 34 (28%) and 39 (32%) patients, respectively. Potential prognostic factors such as ECOG performance status, histology and grade as well as presence of ascites were similarly distributed among any degree of anemic and non-anemic patients ($p > 0.05$). Although not statistically significant, trend toward moderate to severe anemia before starting chemotherapy associated with advanced disease as well as residual tumor after surgery when compared with non-anemic patients were observed ($p = 0.103$ and 0.066, respectively).

Table 1. Baseline Patients' Characteristics

		Pre-chemotherapy Hb levels			p value
		< 10 g/dl N = 34	10-11.9 g/dl N = 66	> 12 g/dl N = 22	
ECOG					
0	52 (42.6)	10 (29.4)	31 (47.0)	11 (50.0)	0.285
1	41 (33.6)	13 (38.2)	23 (34.8)	5 (22.7)	
2	29 (23.8)	11 (32.4)	12 (18.2)	6 (27.3)	
Stage of disease (FIGO)					
Early (I-II)	52 (42.6)	12 (35.3)	27 (40.9)	13 (59.1)	0.195
Advance (III-IV)	70 (57.4)	22 (64.7)	39 (59.1)	9 (40.9)	
Histology					
Serous	43 (35.2)	16 (47.1)	19 (28.8)	8 (36.4)	0.418
Mucinous	8 (6.6)	1 (2.9)	5 (7.6)	2 (9.1)	
Others	71 (58.2)	17 (50.0)	42 (63.6)	12 (53.5)	
Grading					
G1	20 (16.4)	6 (17.6)	10 (15.2)	4 (18.2)	0.379
G2	27 (22.1)	5 (14.7)	14 (21.2)	8 (36.4)	
G3	75 (61.5)	23 (67.6)	42 (63.6)	10 (45.4)	
Residual tumor after initial surgery					
None	51 (41.8)	11 (32.4)	26 (39.4)	14 (63.6)	0.186
≤ 1 cm	14 (11.5)	4 (11.8)	9 (13.6)	1 (4.5)	
> 1 cm	57 (46.7)	19 (55.9)	31 (47.0)	7 (31.8)	
Ascites					
Absent	40 (32.8)	9 (26.5)	23 (34.8)	8 (36.4)	0.647
Present	82 (67.2)	25 (73.5)	43 (65.2)	14 (63.6)	
Platinum-based regimen					
Paclitaxel	70 (57.4)	19 (55.9)	41 (62.1)	10 (45.5)	0.383
Others	52 (42.6)	15 (44.1)	25 (37.9)	12 (54.5)	

Association of hemoglobin levels with treatment outcomes

The overall survival probability was 96%, 76%, and 53% for patients with pre-chemotherapy Hb levels > 12 g/dl, 10-11.9 g/dl, and < 10 g/dl, respectively. Overall survival was significantly related to degree of anemia before starting chemotherapy (p = 0.001) (Figure 1), but this was not the case with Hb levels throughout chemotherapy (p = 0.062) (Figure 2).

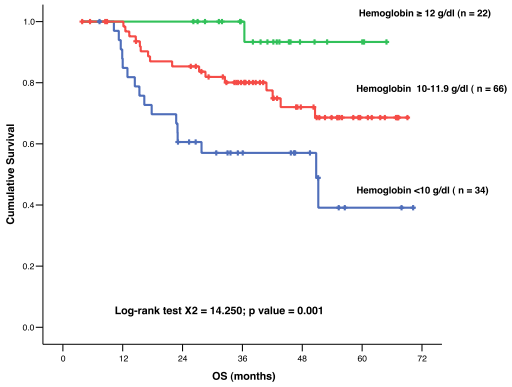

Figure 1. Overall Survival (OS) with Reference to Hemoglobin Levels Before Starting Chemotherapy

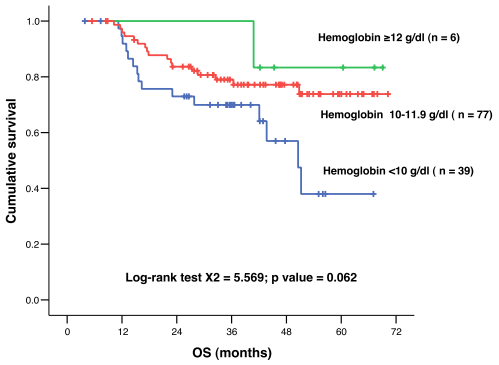

Figure 2. Overall Survival (OS) with Reference to Hemoglobin Levels During Chemotherapy

Correlation among degree of anemia and overall survival are described in Table 2. Univariate analyses demonstrated a significant influence of poor ECOG performance status, advanced stage of disease, residual tumor after primary surgery as well as degree of anemia before starting chemotherapy in term of overall survival (p = 0.01). However in multivariate analyses, the significant prognostic factors on survival could be determined only as residual tumor after primary surgery and degree of anemia before starting chemotherapy (p = 0.013 and 0.015, respectively) (Table 2).

Sensitivity/specificity analyses and Kaplan-Meier studies

At a rate 60% of both sensitivity and specificity, Hb levels before and throughout chemotherapy of 10.5 g/dl and 10.1 g/dl respectively were revealed as the optimal cut-off value to evaluate the prognostic impact in terms of death. The ROCs of both levels were plotted and their AUCs (95% confidence interval) were 0.691 (0.590-0.792) and 0.599 (0.482-0.716), respectively.

Kaplan-Meier analysis demonstrated a significant difference in terms of overall survival between patients with lower and higher Hb levels before starting chemotherapy (p < 0.05). With respect to Hb levels throughout chemotherapy, a borderline significance (p = 0.085) was found. Patients with Hb levels above the determined cut-off level of 10.1 g/dl tended to have a longer overall survival.

Table 2. Univariate and Multivariate Analysis with Regard to Overall Survival

Variable	Univariate			Multivariate		
	HR	95%CI	p value	HR	95%CI	p value
ECOG (2 vs < 2)	2.68	1.33-5.42	0.006	1.23	0.57-2.66	0.599
Stage of disease (advanced vs early)	5.52	2.12-14.37	<0.001	1.31	0.40-4.23	0.657
Grading (3 vs < 3)	0.72	0.36-1.45	0.359	-	-	-
Histologic type (serous vs non-serous)	1.55	0.78-3.08	0.209	-	-	-
Residual tumor (> 1 vs ≤ 1)	8.32	3.20-21.63	<0.001	4.05	1.34-12.18	0.013
Hb before chemotherapy						
Mild anemia vs normal	5.82	0.77-43.96	0.088	5.22	0.68-40.14	0.113
Moderate to severe anemia vs normal	14.11	1.87-106.53	0.010	12.57	1.64-96.45	0.015
Hb throughtout chemotherapy						
Mild anemia vs normal	1.76	0.23-13.26	0.583	1.89	0.25-14.59	0.542
Moderate to severe anemia vs normal	3.73	0.49-28.41	0.203	3.48	0.44-27.56	0.237

HR, Hazard Ratio; 95% CI, 95% Confidence interval

Discussion

Anemia is common in patients with malignant tumors. The prevalence of anemia varies depending on the type of tumor and the cancer therapy administered. Gynecological malignancies are among the tumors characterized by a higher prevalence of anemia at diagnosis (Ludwig et al., 2004). Our data also show a high prevalence of anemia in patients with ovarian cancer before starting chemotherapy (82%).

The impact of anemia on health-related quality of life of cancer patients has been demonstrated by randomized trials and large community based studies (Glaspy et al., 1997; Demetri et al., 1998). Furthermore, numerous studies have shown that the presence of anemia either before or during anticancer treatment is an adverse prognostic factor for survival in patients with cancer (Albain et al., 1991; Caro et al., 2001; MacRae et al., 2002; Van Belle et al., 2003). However, few data are currently available about the clinical relevance of Hb levels before and particularly throughout chemotherapy for patients with primary epithelial ovarian cancer (Obermair et al., 1998; Obermair et al., 2000; Munstedt et al., 2003; Gadducci et al., 2005; Di Maio et al., 2006; Eichbaum et al., 2009). Moreover, there is limited, partially contradictory information in the literature on the prognostic influence of anemia on patients with ovarian cancer undergoing first-line chemotherapy. In the retrospective study (Obermair et al., 1998), 32% of 206 patients with FIGO stage I–IV epithelial ovarian cancer had Hb levels < 12 g/dl in blood samples drawn 24-48 hours prior to surgery. Anemia was found to be an independent poor prognostic variable for overall survival. However, in a subsequent study, pre-operative Hb values proved to be an independent prognostic factor for the 203 patients with stage I–II disease, but failed to attain significance at multivariate analysis in the 350 patients with stage III–IV disease (Obermair et al., 2000).

In 2003, Münstedt et al. studied retrospectively 250 ovarian cancer patients planned to receive at least 6 cycles of chemotherapy. The authors found that Hb levels prior to and during chemotherapy >12 g/dl were associated with prolonged overall survival (P < 0.001) (Munstedt et al., 2003). Gaducci and colleagues demonstrated in a retrospective study of 315 patients with primary epithelial ovarian cancer that decreasing pre-chemotherapy Hb levels are related to an impaired overall survival at univariate but not at multivariate analysis (Gadducci et al., 2005). Di Maio et al. confirmed again in a retrospective study that Hb level prior to chemotherapy was an independent prognostic factor for patients with primary ovarian cancer, but also found correlations between lower Hb levels prior to chemotherapy and other adverse prognostic factors (Di Maio et al., 2006). A recent study by Eichbaum et al. involving patients with primary epithelial ovarian cancer demonstrated that mean Hb levels before and particularly throughout chemotherapy had prognostic impact in terms of relapse in univariate analyses and the mean Hb cut-off levels for prognostic significance on progression-free survival were 11.6 g/dl and 11.2 g/dl, respectively (Eichbaum et al., 2009). Our data are somewhat different from those reported above. By log-rank test, overall survival was related to pre-chemotherapy Hb levels (p = 0.001), but not to Hb levels throughout chemotherapy (p = 0.062). Further analysis showed that pre-chemotherapy Hb level was an independent prognostic factor in terms of overall survival, and the mean Hb cut-off level for prognostic significance on overall survival was 10.5 g/dl (p=0.002). On the other hand, Hb level throughout chemotherapy was not related to the clinical outcome of patients either at univariate or at multivariate analyses. In other words, our present data confirm the previous studies involving patients with ovarian cancer that anemia prior to chemotherapy has prognostic impact on clinical outcome, however, the role of Hb throughout chemotherapy, which was influenced by chemotherapy-induced myelosuppression and anemia correction, remains unclear.

The reason underlying the association between low pretreatment Hb level and poor prognosis has not been fully elucidated. Anemia is a major contributing factor to tumor hypoxia, which occurs when the tumor growth exceeds the ability of the local microvasculature to supply oxygen to the tumor cells (Vaupel et al., 2001). The effects of oxygenation on tumor biology have been long investigated. Höckel et al. measured tumor oxygenation using pO2 polarography and found that pO2 was a useful prognostic factor in patients with advanced-stage cancer of the uterine cervix (Hockel et al., 1996). Emerging evidence indicates that a hypoxic microenvironment can have a major influence on the malignant phenotype of

the tumor and that oxygen may play an important role in the response to cancer treatment (Hockel et al., 2001). In vitro and in vivo experimental studies have shown that hypoxia may provide a selection pressure for tumor cells with higher rates of mutation, which may ultimately result in increased metastatic potential and cellular growth, decreased cell response to apoptosis signals, and therapy resistance (Young et al., 1988; Graeber et al., 1996; Reynolds et al., 1996; Vaupel et al., 2003; Van Belle et al., 2003). Both radiation therapy and chemotherapy were reported to be more effective in well oxygenated than in hypoxic conditions (Hockel et al., 1996; Liang, 1996; Thews et al., 1998). Moreover, anemia itself may induce a feedback mechanism that enhances angiogenesis and leads to a higher proliferation rate of tumor cells (Van Belle et al., 2003).

Another explanation of the prognostic role of anemia is that decrease in Hb level is related to a more aggressive tumor phenotype. Tumor-released cytokines, such as interleukin-1, interferon-gamma, and tumor necrosis factor are known to induce changes in iron metabolism, hemolysis, endogenous erythropoietin deficiency, and suppression of erythroid progenitor cells (Mercadante et al., 2000; Bron et al., 2001; Tas et al., 2002; Dicato, 2003). Cancer-related anemia has been regarded as a paraneoplastic phenomenon. In other words, tumors in patients with anemia may have a considerable number of cell clones that are biologically more aggressive than those in patients with higher Hb levels. Previous studies have shown that cancer-related anemia was correlated with the prognostic factors related to tumor burden (advanced stage and residual disease after primary surgery). Although no such correlation was found in our study, patients with moderate to severe anemia (< 10 g/dl) in our series tended to have more advanced disease and macroscopic residual tumors after primary surgery when compared to those with normal Hb levels (> 12 g/dl).

In conclusion, this study shows that anemia has a prognostic impact for overall survival in ovarian cancer patients candidate to first-line chemotherapy. However, the prognostic influence of decreased Hb levels throughout chemotherapy has still not been satisfactorily clarified and needs to be determined in further prospective studies.

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