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ORIGINAL RESEARCH

Correlation Between Hemoglobin Levels and the Prognosis of First-Line Chemotherapy in Patients with Advanced Gastric Cancer

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Qing Wei*
Xing Yuan*
Qi Xu
Jingjing Li
Lei Chen
Jieer Ying

Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital); Institute of Cancer and Basic Medicine (ICBM), Chinese Academy of Sciences, Hangzhou 310022, People's Republic of China

*These authors contributed equally to this work

Background: This retrospective study evaluated the prognostic significance of hemoglobin (Hb) levels in patients (pts) with unresectable locally advanced or metastatic gastric cancer who have not previously received chemotherapy.

Patients and Methods: We screened 249 pts with advanced gastric cancer, who were categorized into four groups, namely, non-anemia (normal Hb levels), mild (10 g/dl to normal), moderate (8–10 g/dl), and severe anemia groups (<8 g/dl), to study the prognostic significance of Hb levels. We also examined the correlation between changes in Hb levels and treatment effects via imaging during the treatment course.

Results: The objective response rate (ORR) was 47.4% for pts with anemia versus 43.4% for pts without anemia (P=0.536). Hemoglobin levels were reduced by 0.51 ± 1.86 and 1.93 ± 1.33 g/dl after chemotherapy versus before chemotherapy in the disease control group and progressive groups, respectively (P=0.002). The median progression-free survival (mPFS) of first-line chemotherapy in all pts was 6.3 months. Specifically, the mPFS was 5.7 months in pts with severe anemia, compared with 6.4 months for pts with non-severe anemia (Hb≥8g/dl). The median overall survival (mOS) of all pts was 14.0 months. In particular, the mOS was 15.0 months for pts with non-anemia and mild anemia (Hb≥10g/dl) versus 11.5 months for pts with moderate or severe anemia. In multivariate analysis, ascites and decreased Hb post-chemotherapy were identified as independent prognostic indicators for PFS and OS.

Conclusion: Our findings indicate that Hb levels are associated with the prognosis in the first-line chemotherapy for pts with advanced gastric cancer. Pts with progressive disease experience a larger decrease in Hb levels, and those with baseline Hb levels ≥10 g/dl experience longer OS.

Keywords: anemic, hemoglobin, gastric cancer, prognosis

Introduction

Gastric cancer is the fifth most common malignancy globally, and half of all cases occur in Eastern Asia (mainly in China).[1] Patients with gastric cancer are typically diagnosed with stage IV disease, precluding surgical treatment.[2] Anemia is one of the common concomitant diseases of advanced gastric cancer (AGC).[3] The cause is multifactorial,[4] including hemorrhage, hemolysis, nutritional deficiencies, renal insufficiency, hormonal dysfunction, and other factors. Malignant tumors can cause or aggravate anemia via several mechanisms. In particular, cancer cells destroy hematopoietic cells and inhibit hematopoietic function by infiltrating bone marrow infiltration and reducing peripheral hemoglobin (Hb) levels. Blood loss

Correspondence: Jieer Ying
Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital); Institute of Cancer and Basic Medicine (ICBM), Chinese Academy of Sciences, Hangzhou 310022, People's Republic of China
Email jieerying@aliyun.com

caused by tumor sites can further aggravate anemia.[5,6] Other reasons include immune-mediated antibody hemolysis and changes in blood clotting capacity.[7]

Low Hb content is one of the factors affecting the outcomes of pts with AGC. A series of studies confirmed that anemia worsens the prognosis of gastric cancer.[8,9] However, some studies found no correlation between anemia and the outcomes of gastric cancer,[10,11] and thus, the impact of Hb levels on prognosis in pts with AGC receiving first-line chemotherapy remains unclear.

To resolve this issue, our study evaluated the prognostic significance of Hb levels in pts with AGC who have not previously received chemotherapy. Additionally, we explored the relationship between the change of hemoglobin levels following chemotherapy and efficacy in pts with AGC to provide some evidence for improving the prognosis of such pts.

Patients and Methods

Study Population

This study was approved by the Ethics Committee of Zhejiang Cancer Hospital and was conducted according to the principles of the Declaration of Helsinki. As this retrospective study did not harm the rights and health of patients and protected their privacy and personal information, the ethics committee waived the requirement to obtain informed consent. In this single-institution retrospective study, we collected data of 397 pts with unresectable locally advanced or metastatic gastric adenocarcinoma who received first-line chemotherapy at Zhejiang Cancer Hospital between 2006 and 2017 (Figure 1). All pts received at least two cycles of chemotherapy, and measurable lesions were confirmed via imaging. Two hundred and forty-nine consecutive gastric cancer patients were further analyzed. Clinical parameters, including age, gender, Eastern Cooperative Oncology Group performance status, anatomic tumor location, stage of differentiation, Lauren classification, Her-2 expression, liver metastasis, lymph node metastasis, presence of ascites, and initial platelet counts were obtained by reviewing the medical records. Table 1 shows the basic characteristics of the selected pts.

Treatment Regimens

All of the pts received the first-line doublet treatment, chemotherapy regimens include S-1 40–60 mg twice daily on days 1–14 plus oxaliplatin 130mg/m2 on day 1 (N=177, 71.1%), the same dose of S-1 plus cisplatin 60~80mg/m2 on day 1 (N=27, 10.8%), the same dose of S-1 plus paclitaxel 135–175mg/m2 on day 1 (N=13, 5.2%), capecitabine 1000mg/m2 twice daily on days 1–14 plus oxaliplatin 130mg/m2 on day 1(N=29, 11.7%), docetaxel 75 mg/m2 on day 1 and cisplatin 75 mg/m2 on day 1 plus fluorouracil 750 mg/m2/d on days 1–5 (N=3, 1.2%). The above chemotherapy regimens are all 21 consecutive days per cycle. Treatment was continued

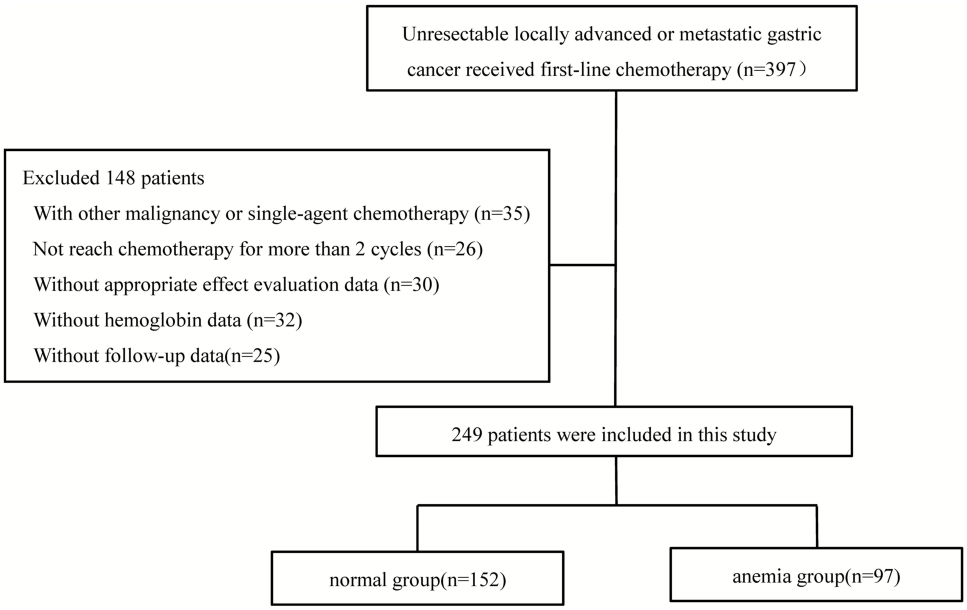

Figure 1 Flowchart of the patient selection for this study.

Table 1 Baseline Information on the 249 Patients with Advanced Gastric Cancer

	N	Non-Anemic Patients	Anemic Patients	χ^2	*P* value
N	249	152	97		
Gender					
Male	155	94(61.8%)	61(62.9%)	0.027	0.868
Female	94	58(38.2%)	36(37.1%)		
Age					
<56	115	75(49.3%)	40(41.2%)	1.565	0.211
≥56	134	77(50.7%)	57(58.8%)		
ECOG					
0–1	217	143(94.1%)	74(76.3%)	16.733	<0.001
2	32	9(5.9%)	23(23.7%)		
Site of gastric					
Lower	85	44(28.9%)	41(42.3%)	5.379	0.146
Upper	51	36(23.7%)	15(15.4%)		
Middle	86	55(36.2%)	31(32.0%)		
Others	27	17(11.2%)	10(10.3%)		
Stage of differentiation					
High-medium	45	25(16.4%)	20(20.6%)	1.536	0.464
Lower	130	84(55.3%)	46(47.4%)		
Unclear	74	43(28.3%)	31(32.0%)		
Lauren classification					
Diffuse	122	79(52.0%)	43(44.3%)	2.100	0.350
Intestinal	117	66(43.4%)	51(52.6%)		
Mixed	10	7(4.6%)	3(3.1%)		
Her-2					
Negative	74	45(29.6%)	29(29.9%)	2.243	0.326
Positive	16	7(4.6%)	9(9.3%)		
Unclear	159	100(65.8%)	59(60.8%)		
Metastatic sites (Liver)					
Negative	162	102(67.1%)	60(61.9%)	0.718	0.397
Positive	87	50(32.9%)	37(38.1%)		
Metastatic sites (lymph nodes)					
Negative	74	51(33.6%)	23(23.7%)	2.746	0.098
Positive	175	101(66.4%)	74(76.3%)		
Metastatic site (Ascites)					
Negative	197	118(77.6%)	79(81.4%)	0.521	0.471
Positive	52	34(22.4%)	18(18.6%)		
Metastatic site (others)					
Negative	154	96(63.2%)	58(59.8%)	0.284	0.594
Positive	95	56(36.8%)	39(40.2%)		
Initial platelet (10^9/L)					
≤80	2	2(1.3%)	0(0.0%)	1.287	0.522
>80	247	150(98.7%)	97(100.0%)		

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

until disease progression, intolerable toxicity, or other reason for termination were judged by the physician.

Assessment

Evaluation of efficacy after 2 cycles of chemotherapy. Tumor response was evaluated according to Response Evaluation Criteria in Solid Tumors 1.1. The objective response rate (ORR) was defined as the percentage of pts who achieved a CR or PR. Statistical analysis of Hb levels was performed using baseline Hb levels before treatment and two cycles after chemotherapy. Anemia was graded according to the National Institute of Cancer Research and Chinese definitions of anemia. Anemia was defined as an Hb level of <11.0 g/dl in females and <12.0 g/dl in males.[12] According to the Common Terminology Criteria for Adverse Events (version 4.0), pts were divided into the non-anemia (normal Hb levels) and anemia group. Then, the anemia group was further divided into mild anemia (10 g/dl to normal levels), moderate anemia (8–10 g/dl), and severe anemia groups (<8 g/dl).

Medical records or telephone inquiries were used to measure the duration of survival or confirm death. Progression-free survival (PFS) was defined as the time from diagnosis of metastatic disease to first occurrence of PD, or death. Overall survival (OS) was defined as the time from diagnosis of metastatic disease to death from any cause or the last date of follow-up (June 30, 2019). At the end of follow-up, 236 pts had died.

Statistical Analysis

Clinicopathological factors were analyzed using Pearson's χ^2 or Fisher's exact test. The relationship between Hb levels and curative effects was examined using Wilcoxon's signed-rank test and Mann–Whitney's rank-sum *U*-test. PFS and OS were estimated using the Kaplan–Meier method. Univariate analysis (UVA) and multivariate analysis (MVA) by a Cox proportional hazards regression model

were used to detect prognostic factors. The statistical significance of survival curves was compared between groups using the Log-rank test. $P < 0.05$ denoted statistical significance in all analyses. All data were analyzed using SPSS 20 statistical software (SPSS Inc., Chicago, IL, USA).

Results

Clinical Pathology

Among the 249 pts, 152 (61.0%) pts had normal Hb levels, whereas 97 (39.0%) pts had anemia, respectively. Eastern Cooperative Oncology Group performance status of 2 was significantly correlated with anemia ($P < 0.001$). No differences were observed between pts with and without anemia in terms of gender, age, site of gastric cancer, stage of differentiation, Lauren classification, Her-2 expression, liver metastasis, lymph node metastasis, presence of ascites, and initial platelet counts (Table 1).

Fourteen (5.6%) pts received red blood cell infusions or erythropoietin treatment, all of whom had severe anemia.

Comparison of Hb Levels Between Pts with and without Anemia

The Hb levels of pts without anemia before and after chemotherapy were 13.35 ± 1.29 and 11.93 ± 1.50 g/dl, respectively. In order to eliminate the influence of 14 pts treated with blood transfusion or erythropoietin on Hb changes, we analyzed Hb levels of 83 anemia pts. The levels among pts with anemia were 9.83±1.17 g/dl before chemotherapy and 10.22±1.27 g/dl after chemotherapy. ΔHb (difference in Hb levels between before and after chemotherapy) was −1.42 ± 1.45 g/dl among pts without anemia, versus 0.39±1.39 g/dl among pts with anemia ($P < 0.001$, Table 2).

Relationship Between Hb Levels and Treatment Effects

Among the 249 pts, CR, PR, SD and PD were recorded in 3 (1.2%), 109 (43.8%), 124 (49.8%), and 13 pts (5.2%), respectively. The ORR was 47.4% (46/97) for pts with anemia, whereas that for pts without anemia was 43.4% (66/152, $P = 0.536$). The Hb level before chemotherapy was not correlated with the treatment effect ($P = 0.353$, Table 3). The Hb levels before and after chemotherapy in the disease control group (CR + PR + SD) were 11.76 ± 2.39 and 11.26 ± 1.67 g/dl, respectively ($P < 0.001$), whereas those in the PD group were 12.72 ± 2.10 and 10.79 ± 1.51 g/dl, respectively ($P = 0.002$). ΔHb was −0.51 ± 1.86 in the disease control group, compared with −1.93 ± 1.33 in the PD group ($P = 0.002$, Table 4, Figure 2).

Table 3 Relationship Between Hemoglobin (Hb) Levels Before Chemotherapy and Treatment Effects

	n	Hb				χ^2	*P* value
		Normal	Mild	Moderately	Severe		
CR	3	2	0	1	0	9.031	0.353
PR	109	64	22	17	6		
SD	124	75	20	15	14		
PD	13	11	0	2	0		

Survival Outcomes

The median progression-free survival (mPFS) for all pts was 6.3 months (95% confidence interval [CI] = 6.0–6.6). All patients were divided into four groups, including normal, mild, moderate and severe anemia group, mPFS was 6.3, 7.2, 6.1 and 5.7 months, respectively (P=0.121, Figure 3A). With 10g/l as the cutoff value, mPFS in patients with non-moderate to severe anemia and moderate to severe anemia was 6.5 and 6.1 months (P=0.152, Figure 3B). With 8g/l as the cutoff value, the mPFS of pts with severe anemia was 5.7 months, which was significantly shorter than that of pts with non-severe anemia (6.4 months, $P = 0.036$, Figure 3C).

The median overall survival (mOS) of all pts was 14.0 months (95% CI 12.7–15.3), compared with four groups, including normal, mild, moderate and severe anemia group, mOS was 15.0, 15.9, 11.9 and 10.8 months, respectively

Table 2 Comparison of Hemoglobin (Hb) Levels Between Pts with and without Anemia

	n	Hb (g/dl)		
		Before Chemotherapy	After Chemotherapy	ΔHb
Normal group	152	13.35±1.29	11.93±1.50	−1.42±1.45
Anemia group	83	9.83±1.17	10.22±1.27	0.39±1.39
P value				<0.001

Table 4 Relationship Between the Changes of Hemoglobin (Hb) Levels and Treatment Effects

	n	Hb (g/dl)		*P* value
		Before Chemotherapy	After Chemotherapy	
CR+PR+SD	236	11.76±2.39	11.26±1.67	<0.001
PD	13	12.72±2.10	10.79±1.51	0.002

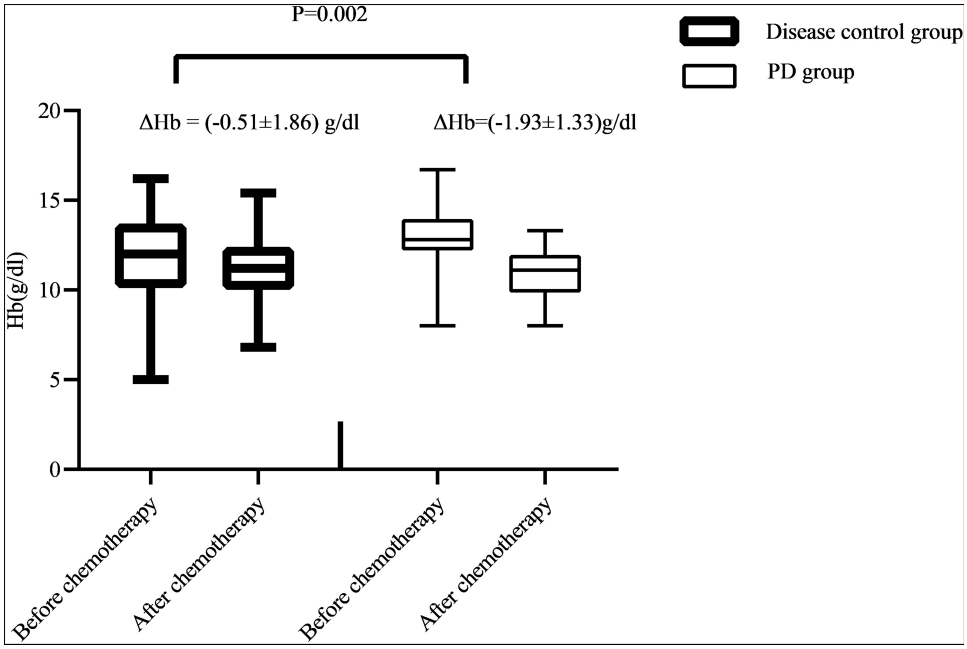

Figure 2 Relationship between the changes of Hb and treatment effects.

(P=0.115, Figure 3D). The mPFS of pts with moderate or severe anemia was 11.5 months, which was significantly shorter than that of pts with non-moderate to severe anemia (15.0 months, P=0.048, Figure 3E). The mOS was 14.6 months for pts with non-severe anemia, versus 10.8 months for pts with severe anemia (P=0.104, Figure 3F).

Further analysis of our data, 14 of 20 patients with severe anemia received EPO or transfusion therapy, and 6 patients did not receive the treatment. mPFS was 5.9 and 4.6 months (P=0.40), mOS was 11.0 and 8.9 months (P = 0.43).

Predictors of Mortality

As for PFS, ascites (P = 0.028) and Hb post chemotherapy (P=0.033) were significantly identified in univariate analysis for PFS (Table 5). In multivariate analysis, ascites (HR=1.374,95% CI: 1.112~1.636, P =0.041) and decreased Hb post chemotherapy (HR=1.201,95% CI: 1.002~1.400, P =0.047) were identified as independent prognostic indicators.

ECOG (P =0.008), ascites (P = 0.001) and Hb post chemotherapy (P=0.031) were significantly identified in univariate analysis for OS (Table 6). In multivariate analysis, ECOG (HR=1.253,95% CI: 1.032~1.522, P =0.023), ascites (HR=1.689,95% CI: 1.220~2.339, P =0.002) and decreased Hb post chemotherapy (HR=1.187,95% CI: 1.072~1.302, P =0.048) were identified as independent prognostic indicators.

Discussion

Our single-institution retrospective study analyzed the associations of Hb levels with treatment outcomes and survival in 249 pts with AGC who received first-line chemotherapy. Our research demonstrated that Hb levels are associated with prognosis. Pts with PD experience a larger decrease in Hb levels, and those with low Hb levels have a poor prognosis.

The results illustrated that a poor performance status was significantly correlated with anemia, which is consistent with the results of other studies.[13,14] This research demonstrated that Hb levels tended to decrease after treatment in pts without anemia, versus an upward trend in pts with anemia. This finding might be related to adverse reactions to chemotherapy in pts with normal baseline levels of Hb.[15] In such pts, the drug damages hematopoietic stem cells and causes anemia. Chemotherapy can also damage the kidneys, thereby decreasing the secretion of erythropoietin and inducing anemia.[16] Meanwhile, among pts without anemia, the tumor inhibits hematopoietic function through the direct invasion of bone marrow. The size of the lesion is reduced by chemotherapy, resulting in improved hematopoietic function and increased Hb levels.

In our study, the ORR of first-line chemotherapy in pts with AGC was 45%, in line with those in the Real-2 study (46.4%)[17] and SPIRITS trial (31–54%).[18] There are few reports on the relationship of changes in Hb levels

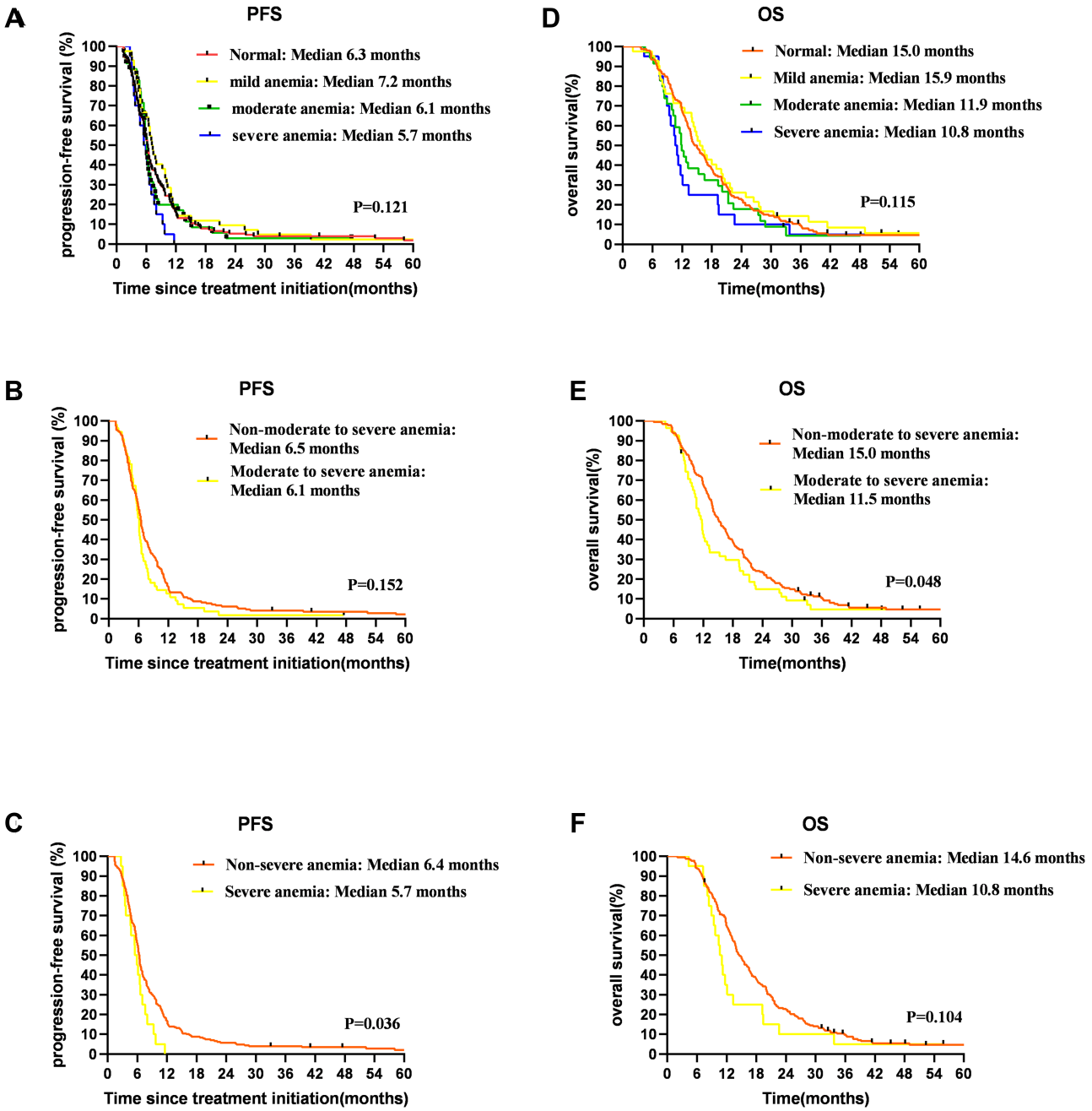

Figure 3 Progression-free survival and overall survival of all patients. (**A**) Kaplan-Meier (KM) survival curves comparing the PFS of patients with normal, mild, moderate and severe anemia group.(**B**) Comparing the PFS of patients with non-moderate to severe anemia and moderate to severe anemia group. (**C**) Comparing the PFS of patients with non-severe anemia and severe anemia group. (**D**) Comparing the OS of patients with normal, mild, moderate and severe anemia group. (**E**) Comparing the OS of patients with non-moderate to severe anemia and moderate to severe anemia group. (**F**) Comparing the OS of patients with non-severe anemia and severe anemia group.
Abbreviations: PFS, progression-free survival; OS, overall survival.

between before and after chemotherapy with efficacy in pts with AGC. Our results illustrated that Hb levels decreased in both the disease control and PD groups. Compared with the findings in the disease control group, Hb levels were significantly decreased in the PD group after treatment. This may be attributed to hypoxic supply of tumor tissue influencing the efficacy of chemotherapy.[19] This result suggests that changes in Hb levels between before and after chemotherapy can predict treatment efficacy.

The relationship between anemia and treatment outcomes has been described by several authors. Park et al[8] reported that pts with baseline Hb levels <10 g/dl had lower response rates and higher risks of death. Ji et al[20]

Table 5 Univariate and Multivariate Analysis for PFS

Variate	N	Univariate		Multivariate	
		HR	P	HR	P
Gender			0.668		
Male	155	Reference			
Female	94	0.944 (0.725~1.229)			
Age			0.564		
<56	115	Reference			
≥56	134	0.927 (0.717~1.199)			
ECOG			0.065		
0–1	217	Reference			
2	32	1.433 (0.978~2.100)			
Site of gastric			0.743		
Lower	85	Reference			
Upper	51	0.389 (0.07~2.156)			
Middle	86	0.979 (0.184~5.209)			
Others	27	0.732 (0.152~3.522)			
Stage of differentiation			0.767		
High-medium	45	Reference			
Lower	130	1.111 (0.785~1.574)			
Unclear	74	1.149 (0.785~1.682)			
Lauren classification			0.313		
Diffuse	122	Reference			
Intestinal	117	0.860 (0.662~1.118)			
Mixed	10	1.299 (0.680~2.481)			
Her-2			0.412		
Negative	74	Reference			
Positive	16	1.334 (0.142~12.496)			
Unclear	159	0.449 (0.120~1.680)			
Metastatic sites (Liver)			0.228		
Negative	162	Reference			
Positive	87	1.179 (0.902~1.541)			
Metastatic sites (lymph nodes)			0.456		
Negative	74	Reference			
Positive	175	0.899 (0.680~1.189)			
Metastatic site (Ascites)			0.028		0.041
Negative	197	Reference		Reference	
Positive	52	1.421 (1.145~1.697)		1.374 (1.112~1.636)	
Metastatic site (others)			0.458		
Negative	154	Reference			
Positive	95	0.905 (0.695~1.179)			
Anemia			0.21		
Normal	152	Reference			
Mild	42	0.837 (0.589~1.188)			
Moderate	35	1.033 (0.707~1.510)			
Severe	20	1.521 (0.937~2.468)			

(*Continued*)

Table 5 (Continued).

Variate	N	Univariate		Multivariate	
		HR	P	HR	P
Hb post chemotherapy			0.033		0.047
Elevated	85	Reference		Reference	
Decreased	164	1.224(1.017~1.431)		1.201 (1.002~1.400)	

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Table 6 Univariate and Multivariate Analysis for OS

Variate	N	Univariate		Multivariate	
		HR	P	HR	P
Gender			0.578		
Male	155	Reference			
Female	94	0.927(0.711~1.209)			
Age			0.604		
<56	115	Reference			
≥56	134	0.934(0.723~1.207)			
ECOG			0.008		0.023
0–1	217	Reference		Reference	
2	32	1.739(1.188~2.546)		1.253 (1.032~1.522)	
Site of gastric			0.259		
Lower	85				
Upper	51	1.073 (0.789~1.459)			
Middle	86	0.859 (0.602~1.225)			
Others	27	0.697 (0.434~1.119)			
Stage of differentiation			0.438		
High-medium	45	Reference			
Lower	130	1.197 (0845~1.696)			
Unclear	74	1.279 (0.874~1.871)			
Lauren classification			0.211		
Diffuse	122	Reference			
Intestinal	117	0.823 (0.633~1.069)			
Mixed	10	1.255 (0.656~2.401)			
Her-2			0.281		
Negative	74	Reference			
Positive	16	0.648 (0.370~1.134)			
Unclear	159	0.988 (0.743~1.314)			
Metastatic sites (Liver)			0.575		
Negative	162	Reference			
Positive	87	1.080 (0.826~1.411)			
Metastatic sites (lymph nodes)			0.775		
Negative	74	Reference			
Positive	175	1.042 (0.788~1.378)			

(*Continued*)

Table 6 (Continued).

Variate	N	Univariate		Multivariate	
		HR	P	HR	P
Metastatic site (Ascites)			0.001		0.002
Negative	197	Reference		Reference	
Positive	52	1.791 (1.300~2.466)		1.689 (1.220~2.339)	
Metastatic site (others)			0.22		
Negative	154	Reference			
Positive	95	0.847 (0.650~1.104)			
Anemia			0.252		
Normal	152	Reference			
Mild	42	0.925(0.651~1.313)			
Moderate	35	1.274(0.872~1.861)			
Severe	20	1.473(0.911~2.380)			
Hb post chemotherapy			0.031		0.048
Elevated	85	Reference		Reference	
Decreased	164	1.274 (1.012~1.536)		1.187 (1.072~1.302)	

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

found that low baseline Hb levels represented an independent negative prognostic factor for OS. However, no correlation between anemia and survival was noted in other studies.[10,11] In terms of ORRs, our study identified no obvious difference between pts with and without anemia. This finding may be related to regional and racial differences and different definitions of anemia. In our study, the median PFS was prolonged in pts with non-severe anemia (Hb≥8 g/dl) compared with severe anemia. Meanwhile, median OS was prolonged in pts with non-anemia and mild anemia (Hb≥10 g/dl) compared with moderate or severe anemia. American Society of Clinical Oncology and American Society of Hematology guidelines[21] recommended starting anemia treatment when Hb levels are less than 10 g/dl. Our findings suggest that OS and PFS tend to prolong after correcting severe anemia, also numerous reports have demonstrated that correcting anemia can improve patient outcomes,[22,23] effective management of anemia is important for treating gastric cancer.[24]

The relationship between low baseline Hb levels and poor prognosis in pts with AGC may be attributable to several factors. Anemia reduces oxygen-carrying capacity of the blood, which leads to hypoxia.[25] Hypoxia can stimulate angiogenesis, which increases tumor aggressiveness.[26,27] Additionally, tumor cells can secrete interleukin-6 and tumor necrosis factor-α, which change the hematopoietic microenvironment and lead to decreases in Hb concentrations.[28,29] Hypoxia can accelerate malignant tumor progression and tumor metastasis through various mechanisms, such as tumor suppressor gene inactivation, changes in gene expression, and clonal selection, thereby increasing resistance to chemotherapy[30] and ultimately resulting in poor long-term outcomes.

Our study is the largest retrospective study of analyzing the relationship between changes in Hb levels and the efficacy of first-line chemotherapy in patients with advanced gastric cancer. This paper not only analyzes the relationship between baseline hemoglobin and objective response rate, but also discuss the correlation between hemoglobin changes and efficacy. Second, the research demonstrates the correlation between different levels of anemia and survival. However, our study had several limitations. First, this report was a single-center retrospective study with a limited sample size and possible incomplete information, resulting in recall bias. Second, it is difficult to rule out the effects of chemotherapy when assessing the correlation between Hb levels and efficacy. Furthermore, some information relevant to anemia such as iron and vitamin B12 levels were not available, preventing a deeper analysis of pts with anemia. To resolve these problems, prospective research is needed in the future.

Conclusions

Our study found that low baseline Hb levels signify a poor prognosis in pts with advanced gastric cancer. Pts with baseline Hb levels ≥10 g/dl have longer OS. Additionally, pts with disease progression experience larger decreases in

Hb level, and the degree of change in Hb levels might be a biomarker for predicting efficacy. Larger samples and more complete data are needed to assess whether early intervention for anemia in pts with advanced gastric cancer can improve prognosis.

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Disclosure

The authors report no conflicts of interest in this work.

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