

Original Article

The impact of hemoglobin level and transfusion on the outcomes of chemotherapy in gastric cancer patients

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Abstract: Objective: To examine the impact of hemoglobin levels in predicting outcomes and evaluate whether transfusion could improve the outcomes of chemotherapy on gastric cancer patients. Methods: A total 310 patients were divided into two groups: high Hb group (Hb >90 g/L) and low Hb group (Hb <90 g/L). A portion of patients in low Hb group received transfusion. The effect of hemoglobin level on the chemotherapy outcomes was determined according to the comparison between patients with high hemoglobin and patients with low hemoglobin without transfusion. The effect of transfusion on the chemotherapy outcomes was evaluated by comparing the two low groups (with and without transfusion). Results: A total of 310 patients were within the study criteria. Among them, 27.7% patients in high Hb group, 44.5% patients in low Hb without transfusion and 27.7% patients in low Hb with transfusion were followed up. The 5-years survival rates of high Hb group, low Hb group without transfusion and with transfusion were respectively 29%, 10% and 8%. The survival rate of patients in Hb group without transfusion was higher. The chemotherapy rates of patients in high Hb group, low Hb without transfusion group and with transfusion group were respectively 32.56%, 42.03% and 18.6%. Conclusion: Low nadir Hb (<90 g/L) during chemotherapy had an effect on the survival and chemotherapy response rate. The chemotherapy outcomes could not be improved through increasing Hb level by red blood cell (RBC) transfusion.

Keywords: Hemoglobin level, transfusion, chemotherapy, gastric cancer

Introduction

Anemia is a common complication in patients in variety of cancer and frequently occurred in gastric cancer. Approximately 41% of patients with advanced gastric cancer (AGC) had a hemoglobin (Hb) level <10 g/dl at presentation [1]. The etiology of cancer-related anemia is multifactorial, potentially including chemotherapy and radiation-induced myelosuppression, bleeding, hemolysis, impaired iron absorption, marrow infiltration by tumor, nutritional deficiencies, and cytokine-mediated anemia of chronic disease [2, 3].

Numerous experimental and clinical studies on the correlation between hemoglobin level and survival showed that low hemoglobin (Hb) levels and treatment outcomes are related in patients with cancers of various organs [4-8].

It has been reported that low Hb levels before and during radiation therapy (RT) were associ-

ated with worse local control and survival in various types of cancer [9-11]. Studies performed in patients with cervical and head and neck cancer have indicated that anemia may be associated with decreased chemotherapy response rates and lower survival [12-17]. Studies of Rades et al [18] and Schafer et al [19] have shown that anemia is an independent prognostic factor which affected the local control rate and survival rate in patients with head and neck squamous cell carcinoma and emphasized that more attention should be paid to the patients with anemia and there was similar results in the studies of cervical and endometrial [20, 21].

RBC transfusion has been a mainstay treatment of anemia associated with cancer therapy. Large retrospective studies involving patients with different kinds of cancer who received a variety of chemotherapy regimens have reported that 5% [22, 23] to 33% [24, 25] of patients required RBC transfusion in the

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Table 1. Characteristics of patient and tumor

	High Hb group	Low Hb without transfusion group	Low Hb with transfusion group	All patients	P_1 value	P_2 value
Gender					0.7101	0.2639
Male	60	93	64	217		
Female	26	45	22	93		
Age					0.9689	0.3320
Median	55.5	54	56.5	55		
Range	17-78	24-91	30-85	17-91		
TNM Stage					0.0314	0.1777
I+II	15	11	3	29		
III+IV	71	127	83	281		
Operation					0.0053	0.3087
No	16	52	40	108		
Radical	56	62	30	148		
palliative	14	24	16	54		
EPO					<0.0001	0.1212
Yes	9	56	44	110		
No	77	82	42	200		
Stage of differentiation					0.013	0.4834
Fetal and Poorly differentiated	41	72	42	155		
Moderately differentiated	25	18	14	57		
Well-differentiated	0	3	0	3		
No date	20	45	30	95		
Unknown	2	2	2	6		
Chemotherapy regimens					0.0028	0.8580
Based on 5FU	24	27	17	68		
Based on Paclitaxel	8	39	28	75		
5-FU and Paclitaxel	48	69	40	157		
Others	6	3	1	10		

P_1 : Comparing difference between the two non-transfusion groups (High Hb group vs Low Hb without transfusion group); P_2 : Comparing difference between the two low Hb groups (Low Hb without transfusion group vs Low Hb with transfusion group).

treatment of chemotherapy. Even though Hb level has been known to be prognostic, it is still unclear whether raising Hb level by transfusion can directly impact the outcomes of chemotherapy. It is controversial that raising Hb by transfusion could improve chemotherapy or radiotherapy treatment outcomes in cancer patients. Studies have found that RBC transfusion achieving Hb level above 10 g/dl might contribute to the improvement of the Karnofsky (KPS) and quality of life (QOL) seen in patients with advanced gastric cancer (AGC) [2]. Furthermore, it has been reported that transfusion prior to radiation treatment did not improve the outcome in patients with Head And Neck Squamous Cell Carcinoma (HNSCC) and low hemoglobin values, there might be a negative impact on survival [3, 26]. RBC transfusion prior to chemotherapy had no prognostic role in terms of response rate and survival [1].

In our study, in order to clarify the relation of hemoglobin level during chemotherapy and treatment outcomes, we collected data retrospectively from 310 patients and evaluated the impact of the nadir hemoglobin level during chemotherapy on outcomes and survival. Moreover, we also evaluated about whether raising Hb could improve the survival rate. To examine that, we compared the survival rate of anemic patients (<9 g/dl) with and without transfusion.

Methods

Eligibility and patients selection

A prospective study was conducted in this trial. We collected the data retrospectively from 310 patients with adenocarcinoma of stomach who treated with chemotherapy and followed up in

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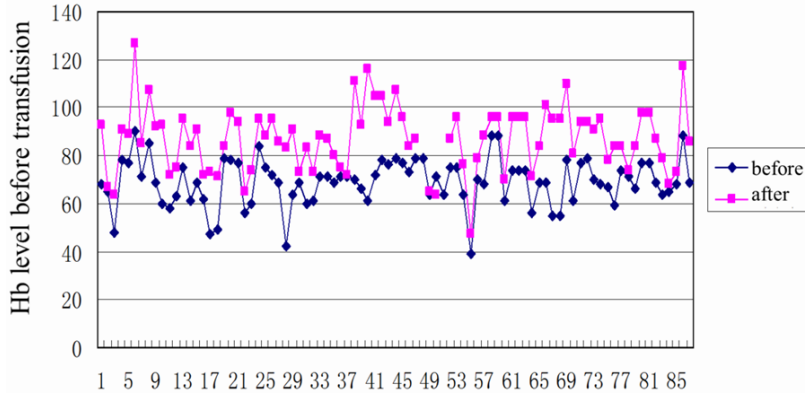


Figure 1. The change of Hb level between after and before transfusion in 86 patients.

Fujian Provincial Cancer Hospital. Patients meeting the following criteria were enrolled: (1) adult patients with a confirmed pathological diagnosis of gastric adenocarcinoma; (2) patients who received chemotherapy treatment in our hospital; (3) these patients with normal liver and kidney function had no prior radiotherapy. Patients with neoadjuvant chemotherapy were included in this analysis. Patients who received less than 3 chemotherapy cycles were excluded in this study.

These patients were divided into three groups: high Hb, low Hb without transfusion and low Hb with transfusion according to the nadir hemoglobin during chemotherapy and transfusion. Patients in high Hb group had the nadir hemoglobin above 9 g/dl. Other patients whose nadir hemoglobin was below 9 g/dl were divided into groups according to whether they had received transfusion or not.

Treatment and assessment

All patients received first-line chemotherapy for metastatic and/or recurrent gastric cancer. The chemotherapy regimens included single agent paclitaxel and 5-FU combinations of paclitaxel or platinum.

Except for the patients who could not tolerate operation, all patients received palliative operation or radical surgery. In purpose of discussing whether transfusion could improve the outcomes of chemotherapy in patients with gastric cancer, Hb level of 9 g/dl was used as a cut-off value for further analyses. Hb value was examined every 3-4 days during chemotherapy

cycles. The nadir value was chosen for evaluating the relation between Hb level and chemotherapy response.

Tumor response was evaluated according to World Health Organization criteria [27] and was assessed by abdominopelvic computed tomography scan and other tests that were used initially to determine the stage of tumor.

Statistical analyses

Statistical analyses were performed using the SPSS 19.0 software package. Patient characteristics were compared with chi²-test. The actuarial values of endpoints were evaluated by the Kaplan-Meier plots and compared with log-rank test for equality of survivor functions. The *p*-values were estimated for a two tailed test and *P*<0.05 was considered to be significant difference.

A multivariate Cox proportional hazards analysis was used to evaluate prognostic factors and treatment with respect to the risk of overall survival. Parameters were included in statistically significant univariate analysis. Data are presented as 5-year actuarial hazard ratios (HR) with 95% confidence intervals.

Results

Patient characteristics and treatment

Patient characteristics are shown in **Table 1**. The analysis included 310 eligible and evaluable patients. Their median age was 55 years, among them, 271 were male (87%) and most of them were in cancer stage III and IV. A total 121 of 310 patients did not get surgery because of their inoperable cancer. In order to prolong lifetime, patients underwent palliative or radical operation. More than half of the patients were treated with recombinant human erythropoietin to improve the phenomenon of anemia. No patients in the high hemoglobin group were assigned to receive RBC transfusion, while 86/224 in the low hemoglobin group received transfusion at one occasion.

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Table 2. Chemotherapy response in all groups

	High Hb group	Low Hb without transfusion group	Low Hb with transfusion group	All patients	P_1 value	P_2 value
Chemotherapy response					0.3465	0.0051
CR+PR	28	58	18	104		
SD+PD	56	78	66	200		
Unknown	2	2	2	6		

P_1 : Comparing difference between the two non-transfusion groups (High Hb group vs Low Hb without transfusion group); P_2 : Comparing difference between the two low Hb groups (Low Hb without transfusion group vs Low Hb with transfusion group).

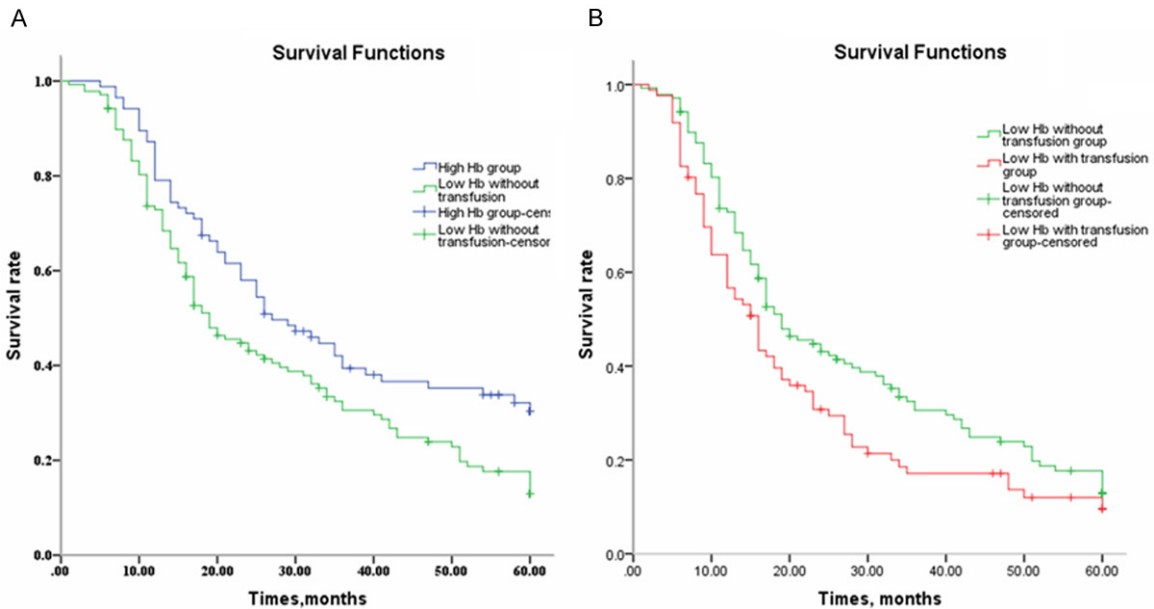


Figure 2. Overall survival probability curves (Kaplan-Meier method) according to hemoglobin group (A) and transfusion group (B).

Transfusion

A total number of 86 patients received RBC transfusion. The Hb level before transfusion ranged from 3.9 g/dL to 9 g/dL. The changes of Hb level before and after transfusion were illustrated in **Figure 1**.

Chemotherapy response rate

Because of the absence of tests or early discontinuation of treatment, 6 of 310 patients could not be evaluated for responses. Responses to chemotherapy were noted in 104 evaluable patients (33.5%) and there were 6 patients with complete responses. The chemotherapy rates of patients in high Hb group, low Hb without transfusion group and low Hb with transfusion group were respectively 32.56%, 42.03% and 18.6%. Comparing with patients in low Hb with transfusion group, patients in low Hb without transfusion group was significantly

less likely to respond to chemotherapy ($P=0.0051$) (**Table 2**). Meanwhile, the chemotherapy rate of patients in low Hb without transfusion group was not significantly more than that in high Hb group ($P=0.3465$).

Survival

Of the 310 patients analyzed in the study, 235 (75.81%) died. The estimated over survival (OS) was 5.2 months. The 1, 3 and 5 years OS were respectively 70%, 44% and 15%. The 5 years OS rate of patients in high Hb group, low Hb without transfusion group and low Hb with transfusion group was 29%, 10% and 8% respectively. The Kaplan-Meier estimate of OS was shown in **Figure 2**.

Variate analysis

Univariate analysis showed statistical significance of Hb level, transfusion, TNM stage,

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Table 3. Univariate analysis in relation to survival

		Chi-Square	P	Hazard Ratio	95% Hazard Ratio	
Hb level	>9 g/dL vs <9 g/d	12.4158	0.0004	0.584	0.433	0.787
Transfusion	transfusion vs non transfusion	12.0022	0.0005	1.636	1.238	2.162
Gender	male vs female	0.0002	0.989	0.998	0.755	1.319
Age		1.1084	0.2924	0.994	0.984	1.005
TNM stage	I+II vs III+IV	37.844	<.0001	1.951	1.577	2.415
Operation methods		65.003	<.0001	0.547	0.472	0.633
EPO	yes vs no	1.5589	0.2118	0.845	0.648	1.101
Chemotherapy regimens 1		4.3176	0.0377	0.743	0.561	0.983
Regimens 2		0.2669	0.6054	0.926	0.69	1.241
Stage of differentiation		6.0305	0.0141	0.627	0.432	0.91

Table 4. Multivariate analysis in relation to survival

		Chi-Square	P	Hazard Ratio	95% Hazard Ratio	
TNM stage	TNM	13.4209	0.0002	1.523	1.216	1.908
Operation methods		31.8383	<.0001	0.627	0.533	0.738

operation methods and stage of differentiation at inclusion (**Table 3**). Using the endpoint of OS probability, patients with Hb >9 g/dl had a better outcomes compared to those with Hb <9 g/dl (HR 0.58; CI 0.433-0.787; P=0.0004). We also found similar result between patients with and without transfusion (HR 1.636; CI 1.238-2.162; P=0.0005).

Multivariate analysis confirmed the importance of TNM stage and operation methods for the endpoint of OS whereas neither Hb level nor transfusion could be identified as independent factors of outcomes (**Table 4**).

Discussion

As reported in studies, anemia had incidence rates ranging from 2% to 78% for solid tumors [28]. Decreased hemoglobin counts could give a rise to several symptoms such as fatigue, exhaustion, and impaired quality of life [29], and may worsen disease prognosis [30, 31]. Hemoglobin levels are currently the focus of interest as prognostic factors in patients with gastric cancer. It has been confirmed in clinical studies, hemoglobin had a significant influence on survival in patients treated with chemotherapy or radiotherapy. In patients with AGC, baseline Hb level was one of the most important adverse prognostic factors for chemotherapy response and survival [1].

Few studies are currently available for the clinical relevance of Hb levels throughout chemotherapy for patients with gastric cancer. This study confirmed the prognostic importance of hemoglobin level during chemotherapy. In the present study, patients with hemoglobin level above 9 g/dL had a higher survival rate than those below 9 g/dL. In previous trails, the hemoglobin levels were generally set too high. For instance, Camilla Molich Hoff et al set females hemoglobin levels above 13.0 g/dL and males above 14.5 g/dL [32]. Jennifer Montgomery et al employed the standard definition of anemia in cancer patients-less than 12 g/dL for both male and female patients [33]. In this study, the cut-off hemoglobin level was set as 9 g/dL. Because of the deficiency blood resources in China, fewer patients with chemotherapy and radiotherapy could receive transfusion unless their hemoglobin level was <9 g/dL. In this study, it has been found that the hemoglobin level was a significant prognostic factor in univariate analysis for OS rate, but we didn't get similar results in multivariate analysis. One reason of this phenomenon may be because there were insufficient patients eligible for this study. The final conclusion is in accordance with the results of the DAHANCA 5 study which also demonstrated univariate prognostic importance of hemoglobin level and no benefit of transfusion [32, 34].

Several mechanisms illustrate the reason why anemia is related to survival rate of cancer patients with chemotherapy or radiotherapy. Experimental results in animal model have shown that tumoral tissues were hypoxic in the

presence of anemia [35]. A lower Hb level is associated with decreased oxygen carrying capacity of erythrocytes, which results in tissue hypoxia [36]. Cells undergo a variety of biological responses when placed in hypoxic conditions, including activation of signaling pathways that regulate proliferation, angiogenesis and death. In order to survive and even grow under hypoxic conditions, cancer cells have adapted these pathways mentioned above [37].

For patients receiving chemotherapy, the increasing hemoglobin level is of great importance for improving survival and chemotherapy rate of cancer. Treatment options included RBC transfusion, ESAs administration, oral or intravenous iron supplement, and a combination treatment. EORPC guidelines endorse early initiation of treatment with erythropoietic growth factor at Hb levels of 9-11 g/dL [38]. There are currently insufficient data available to determine the impact of erythropoietic growth factors on survival in cancer patients. In this study, EPO was demonstrated not a prognostic factors. RBC transfusion is a direct and effective approach to improve the Hb level, however, it is possible that a negative interaction could occur between transfusion and chemotherapy. According to several guidelines, anemia treatment should be started when the Hb levels declined to a certain value. American Society of Clinical Oncology and the American Society of Hematology (ASCO/ASH) guidelines recommended starting anemia treatment when Hb levels declined to 10 g/dl or less than that [39]. NCCN guidelines version 2.2014 Cancer and chemotherapy-induced Anemia recommended chronic anemic patients without acute coronary syndrome was to maintain at a level of Hb 7-9 g/dL [40]. In this study, during chemotherapy, patients with a low hemoglobin level transfusion were able to raise the hemoglobin level, however, the effect of chemotherapy could not be improved by the increasing hemoglobin level. There was a significant improvement in 5 years survival rate. Chemotherapy response rate between low Hb without transfusion group and low Hb with transfusion group was also improved in our study.

It could not be confirmed by Fles et al using the intention-to-treat principle that transfusion could decrease the recurrence and increase the treatment rate [34, 41]. The observation

was found that RBC transfusion prior to chemotherapy had no prognostic role in terms of response rates or survival [18].

There were several potential reasons to explain the phenomenon that RBC transfusion was not beneficial to improving survival. The tendency of worsening the prognosis when receiving transfusion during chemotherapy could be explained by patients with transfusion in the process of treatment, having a worse overall condition and a lower hemoglobin level. Animal studies have demonstrated that hypoxia couldn't be completely eliminated by transfusion or erythropoietic growth factors [42, 43]. The fact that transfusion have been shown to reduce the immune system may relate to the poor survival in patients with transfused cancer. It was not fully evaluated about whether the immune system had functions towards the growing cancer. In cancer patients this immune regulatory effect may be all but beneficial.

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Disclosure of conflict of interest

None.

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